ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 13

Published by
The Association for the Study of Internal Secretions
Suite 1214 Wilshire Medical Bldg.
Los Angeles, Calif.
1929

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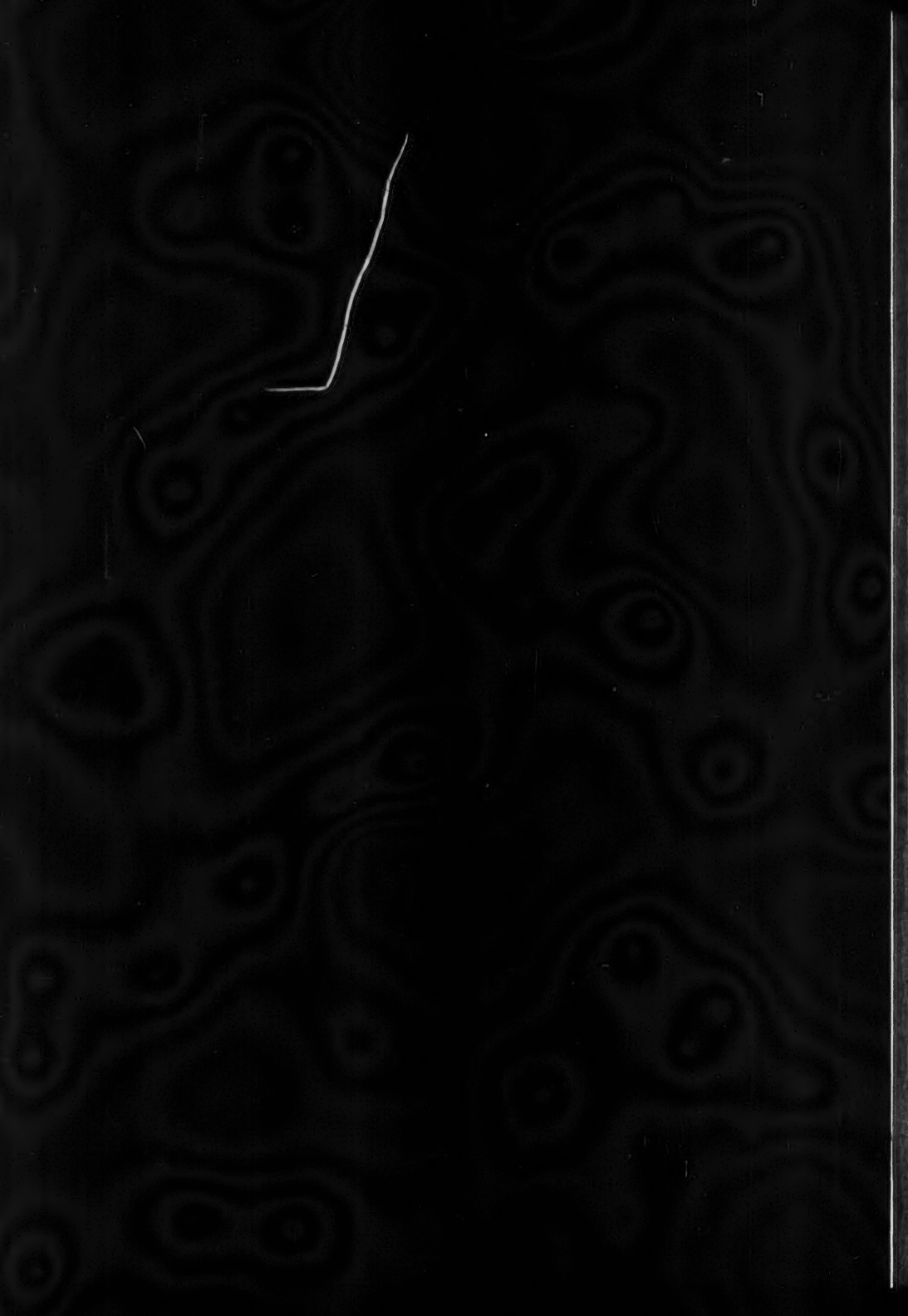

VOLUME 13 NUMBER 1

ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION
FOR THE STUDY OF

INTERNAL SECRETIONS

EDITORS

R. G. HOSKINS, Boston

M. O. LEE, Boston H. LISSER, San Francisco

JANUARY-FEBRUARY

1929

PUBLISHED BI-MONTHLY BY THE ASSOCIATION FOR THE STUDY OF INTERNAL SECRETIONS, SUITE 1214 WILSHIRE MEDICAL BLDG., LOS ANGELES, CALIFORNIA
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Vol. 13. No. 1. Serial No. 63 *January-February, 1929*

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Entered as second-class matter March 12, 1921, at the postoffice at Los Angeles, California, under the Act of March 3, 1879.

Acceptance for mailing at special rate of postage provided for in Section 1103, Act of October 3, 1917, authorized September 17, 1920.

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Every branch of medicine is represented. The orthopedist recognizes the importance of the internal secretions in relation to the physiology and pathology of bone development. The ophthalmologist realizes the relation of the pituitary and the thyroid glands to his field; the pediatrician is especially interested because growth and development are controlled by hormones, and many disorders of childhood are due to, or aggravated by, disturbances of the endocrine glands. Many disorders seen by the gynecologist are brought about by endocrine defects, and there is a large and increasing literature dwelling upon the diagnostic and therapeutic phases of this subject. In internal medicine and surgery the endocrine glands figure constantly. Endocrinology, in short, is a matter of concern to the medical profession as a whole.

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Manuscripts of three types of original work are desired for publication:

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c. *Laboratory investigations* of endocrine problems.

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Manuscripts may be submitted in any modern language, and if found suitable for publication will be translated into English without expense to the authors. To insure a version, however, satisfactory to the author, it is desirable that the article be submitted, when feasible, in English.

Readers who encounter articles of endocrine interest in unusual periodicals or under captions not indicating such interest are requested to submit abstracts for publication.

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THIS NUMBER AND THE NEXT

In presenting this number of ENDOCRINOLOGY to you, we do so with the anticipation that the changes which you notice may all be pleasing and agreeable to you. Considerable time and thought have been given to making such changes as would make our journal more acceptable in every way. The larger size page will enable us to reproduce to better advantage some illustrations and tables which have had to be scaled down in the past. The new cover has been selected with a view to its neat appearance even after considerable use. Altogether, we hope that these changes may be acceptable to our readers and would appreciate any constructive comments which you may wish to make.

The papers in this number will be found to be of interest. Those of the next number will include the seventh of the series by Drs. Rowe and Lawrence.

Drs. Cervera and Torres-Carreras, of Barcelona, will present some reflections on a case of dystrophia adiposo-genitalis; and Dr. Christiansen, of Copenhagen, has a paper on macrosomia adiposa congenita, a new dysendocrine syndrome of familial occurrence, and Dr. Shapiro discusses endocrine disturbances among high school boys, particularly adiposo-dystrophia genitalis.

Drs. Shepardson and Anderson, of San Francisco, report a case of diabetic coma with marked hyperglycemia, and Dr. Rowe, of Detroit, presents another of his studies on oxytocin and vasopressin.

THE PORTLAND MEETING

Arrangements for the program at the Portland meeting are rapidly being completed. We are able to make a preliminary announcement of a part of the papers which will be presented, as follows:

Recent Biochemical Investigations on Extracts of Testes, Fred C. Koch, Chicago.

A Summary of 1000 Glucose Tolerance Tests, Henry J. John, Cleveland.

Some Aspects of the Mode of Action of the Betahormone of the Pituitary, Oliver Kamm, Detroit.

Normal Weight, Height and Proportions (Endocrinologic Interpretation), Wm. Engelbach, St. Louis.

Nasal Spray Method of Administering Hormones of the Ovary and Pituitary Gland, J. P. Pratt and Merrill Smeltzer, Detroit.

Geographical Factors of Calcium Metabolism, Homer Wheelon, Seattle.

Endocrine Regulation of Reproduction, Oscar Riddle, Cold Spring Harbor, N. J.

The Association of Diabetes Mellitus and Diabetes Insipidus, Frank N. Allen, Rochester, Minn.

Other papers are being prepared by Dr. Blair Holcomb, of Portland, and Drs. H. C. Shepardson and H. Lisser, of San Francisco, but the definite titles have not been received.

This meeting will be held in the Auditorium at Portland, Tuesday, July 8, 1929. A further announcement will appear in the next issue of ENDOCRINOLOGY.

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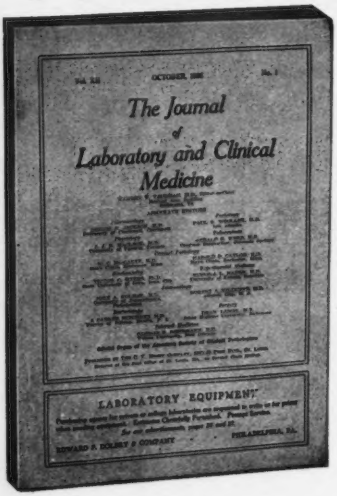
Published first of each month. Volumes begin with October of each year. Subscriptions may begin at any time. $8.50 per year under domestic postage, including the United States, Cuba, Mexico, Porto Rico, Canal Zone, Hawaii, and Philippines. Under Canadian and foreign postage, $8.90. Single copies, 75 cents.



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VOL. XIX. No. 2
(Issued 12th December, 1928)

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ENDOCRINOLOGY

THE BULLETIN OF THE ASSOCIATION FOR THE STUDY OF

INTERNAL SECRETIONS

Volume 13, Number 1 JANUARY-FEBRUARY, 1929 Serial No. 63

STUDIES OF THE ENDOCRINE GLANDS

V. The Adrenals

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AND

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Evans Memorial,

BOSTON, MASS.

In a series of previous papers the authors have described an objective method for the diagnosis of endocrine disorders (1) and the results obtained from its application to several of the recognized members of the endocrine group (2). The present paper presents the results which have been obtained with the few adrenal cases which we have been privileged to see. Contrary to the relative frequency with which pituitary, thyroid, and ovarian disorders are encountered, demonstrable adrenal disease seems to be of very rare occurrence. Osler (3) saw only seventeen cases of Addison's disease in the course of twenty-one years. Boothby and Sandiford record but thirteen Addisonians in a series of two thousand four hundred and seventeen (2417) cases studied at the Mayo Clinic. As they report over six thousand thyroid cases in a parallel series, the relative infrequency is strikingly illustrated, particularly as these two groups are drawn from material many times as extensive. In other words, cases presenting the classic signs of adrenal disease as described by Addison, are most infrequently encountered. That the syndrome is implicit in disturbed function of the adrenal glands is generally accepted, although Lewin's (5) collected series of five hundred and sixty-one cases included 12 per cent without demonstrable lesion, a finding frequently recorded by other and later observers. Further, opinion is by no means unified today as to the relative importance of the cortical and medullary portions in determining the disease picture. In spite of these and other seemingly contradictory observations, the intrinsic association of lowered adrenal activity with the Addisonian syndrome may be regarded as definitely established. A similar authority does not obtain for that other type of adrenal failure which is assumed to result from a lowered functional activity and to be unassociated with gross anatomical changes in the gland. This syndrome, possessing many of the characteristics of Addison's dis-

ease such as asthenia, hypotension, and usually emaciation, has been in large measure developed by the work of the French clinicians, [See among others, Sergent (6) and Lucian and Parisot (7)], while in this country, Sajous (8) has been the earliest and major contributor in defining this condition. Incidentally, it should be said that this syndrome more nearly equates with the picture of adrenal insufficiency as produced in numberless animal experiments involving interference but not complete extirpation. A complete Addisonian has yet to be produced experimentally. A third type of failure, chiefly associated with suprarenal hemorrhage, is an acute condition usually terminating fatally in a few days. In addition, a variety of intermediate states have been described but they lack clarity of outline, and in many instances depend upon a mass of wholly unproven assumptions for their very existence. Of the many so-called pluriglandular syndromes, in largest measure also the work of the French school although clinicians of all nations have synthesized diverting combinations of impressive intricacy, but little notice need be taken. The endocrine glands severally and individually are among the potent regulators of general metabolism. In the impairment of one, as in a similar condition with any of the equally important non-endocrine factors, havoc is wrought in many of the delicately balanced equilibria associated with normal function. In the disturbances thus engendered, it is inevitable that other endocrine as well as non-endocrine foci will participate, and in their several dysfunctions influence the terminal disease picture. But their participation is secondary and resultant, not primary and causative. To illustrate, the amenorrhoeas of thyroid and pituitary failure need not derive from the primary failure of the endocrine activity of the ovary any more than when the condition arises in non-endocrine disease wholly unassociated with the generative system. The use of ovarian extract to combat this condition is as illogical as it is ineffective.

In the preceeding paper in this series we analyzed the 22 pluriglandular cases which have come under observation in the course of examination of nearly four thousand patients. It is enough to say here that with but minor exception the pluriglandular element derives from the superposition of surgical ablation of one gland upon the functional disturbance in another. In a single case, unique in our experience, we observed both a surgical dysthyroid state and partial castration added to a probable pituitary dysfunction, which was seemingly the original endocrinopathy.

Reverting to the immediate thesis, we find a well established entity in Addison's disease and one equally demonstrable in the acute and rapidly fatal condition, deriving from hemorrhage in the gland. Of the third for which, of the many presenting, we will select the term "hypo-adrenalism," there is a less certain foundation of proven and tested fact, yet enough authoritative observations exist to render consideration necessary.

Frank under-function would seem to connote the existence of an antithetical picture in which a complementary over-activity of the gland is manifest. In the earlier paper on the gonads (2) we have recorded our

failure to observe such a condition in our cases involving the primary sex organs. With the adrenal, however, several well marked and rather striking anomalies are frequently associated with alleged hyperactivity of the gland, and brief analysis of these is germane to the text.

Precocious puberty is frequently associated with tumors of the adrenal cortex, and the assumption made that hypernephromata condition on overactivity of the gland. Unfortunately for clarity of definition, the same series of somatic and functional changes have been associated severally with the thymus, pineal, the gonads themselves, and less dubiously, the anterior lobe of the pituitary.* The lack of etiological specificity here greatly enhances the difficulty of the diagnostic problem. Tumor development in adult years is believed to result in an inversion of sex characteristics to which the term "virilism" is usually applied. Cases are also recorded in the pre-adolescent period. The condition is largely confined to the female sex and is intrinsically a masculinization of the secondary sex charactertistics. It should not be confused with precocious puberty which is, as the name implies, an abnormally early maturation along wholly normal lines. Virilism connotes an inhibition of the exocrine manifestations of the sex involved. Modification in the differential sex distribution of body hair (hirsutism) is but one item in the general picture of virilism. It may occur alone, however, or at least without well marked evidence of the other features of a true virilism. It has frequently been recorded in connection with ovarian changes, and it is interesting to note that in the eight cases cited by Falta (9) to associate hirsutism with tumor of the suprarenal, five patients had coincident pathologic changes of the ovary, one "small" ovaries, and in the case of the other two no statement is made concerning the gonads.

Another genital anomaly presenting diverse manifestations is pseudohermaphroditism. True hermaphroditism has never been certainly observed in man. Burden (10) records a case with independent ovaries and testes on each side and Neugebauer (11) cites only five established cases of a single ovotestis. Neumann (12) has recorded some later cases in which there may be a larger measure of support for the thesis but he is skeptical of the accuracy of the conclusions drawn by the authors in many of the cases which he cites. Falta seemingly regards the condition as possibly arising from aberrant adrenal function, a position which has apparently been rather generally adopted [Glynn (13)]. To support his thesis, Falta cites the fact that Neugebauer, in his comprehensive work on the subject, records thirteen cases showing disorder of the adrenals. Inasmuch as Neugebauer records over twelve hundred observations, and further, as in this series he reports sixteen cases each showing neoplasm of ovary or testis, the warrant for so sweeping a generalization would seem to be lacking. Further, several of Falta's quoted supporting cases showed simultaneous involvement of the gonads. The rare conditions

*The literature is fairly extensive, and excellent summaries are to be found in several texts, which emphasize the clinical aspects of endocrine disorders.

designated as "progeria" [Gilford (14)] and "nanism type senile" [Variot and Pironneau (15)] would seem to have but tenuous claim to a purely suprarenal etiology. To summarize then, while the adrenals apparently exercise some influence over the genital sphere, it is far from well defined and is very far from being a unique attribute of this member of the endocrine group. Further, the a priori assumption that cortical tumors determine an over-activity, but ill equates with the observations of neoplasms of the thyroid or pituitary. Lastly, those pictures which may with most certainty be correlated with adrenal disease fail signally to present a uniform antithesis to that offered by the established failure producing Addison's disease.

As the adrenal is essentially two glands, there should be several dysfunctional possibilities, and conceivably certain of the conditions already touched upon could fall in this category. Unfortunately our knowledge of adrenal disease in man is very limited, and the essential nature of its function precludes those surgical interventions that have done so much to clarify our knowledge of certain of the other endocrines. There is, of course, a vast number of most interesting and informative data in relation to animal experiments. As the vast majority of these were designed to throw light on certain physiological problems, data that are applicable to clinical conditions are in the nature of by-products. Further, as we have emphasized in earlier writings, the metabolic divergences of the several species make difficult if not impossible an equation with man. Finally, the results of acute experiments cannot be translated into terms of the chronicity of human disease. Happily, Addison's disease is a rock in the troubled sea of conjecture, surmise, and assumption, and its study offers a sure line of approach to the better comprehension of one phase of disturbed adrenal function. The carefully recorded clinical and laboratory studies of this condition are of the greatest value.

Turning to our own brief series, we must acknowledge initially some difficulty in classifying all of the composing members. Accepted opinion warrants the designation of the Addisonians as hypofunctional cases (I). Far less clear cut are the indices of functional level in the few other cases

TABLE I.

CLASSIFICATION OF CASES

I	Addison's Disease	3
II	Hypo-adrenalism, probable	6
	Hypo-adrenalism, possible	3
III	Pubertas Praecox	1
	Total	13

(II) that we record. In one or two even, doubt exists as to the warrant of inclusion with the seemingly established adrenal cases. As they conform, however, to the criteria established, and as further, they have shown inter-

esting response to the exhibition of adrenal medication (to be discussed later), we feel that they may be included with a frank statement of their dubious character. A single case of "pubertas praecox," seemingly deriving from an adrenal condition, constitutes a third group (III). For the sake of clarity, the composition of the series may be tabulated and in the subsequent summaries the data from each group will be collated separately.

We have had contact with two other cases of Addison's disease (one of them without pigmentation but with diagnosis verified at autopsy). As they were not completely studied, they are omitted from the series. Such measurements as were obtained, however, are in strict accord with those of the cases reported.

TABLE II

Physical Measurements

Observation		I	II	III
Sex	Male	1	3	0
	Female	2	6	1
Age	High (yrs.)	61	62	
	Low (yrs.)	32	22	
	Average (yrs.)	**47**	**38**	**7¾**
Height	High (cm.)	177	175	
	Low (cm.)	158	154.5	
	Average (cm.)	**166**	**165**	**115**
Sitting Height	High (cm.)	92	96	
	Low (cm.)	85	84	
	Average (cm.)	**87**	**88**	**64**
Sitting Height	Index Average	**0.524**	**0.533**	**0.557**
Chest	High (cm.)	80	107	
	Low (cm.)	69.5	61	
	Average (cm.)	**73.5**	**75**	**56**
Weight	High (kgm.)	61.4	89.0	
	Low (kgm.)	48.0	34.8	
	Average (kgm.)	**53.2**	**56.0**	**22.0**
Area	Average (sq. m.)	**1.57**	**1.60**	**0.82**
Lung Volume	High (cc.)	2200	4100	
	Low (cc.)	1820	2100	
	Average (cc.)	**2040**	**3060**	**1700**

Following the practice of the earlier papers, the physical measurements and certain other statistics are presented in Table II. If the values tabulated here be compared with those summaries given in the first endocrine paper (1), it will be noted that certain discrepancies appear. These derive from the fact that the two groups are not identical in composition, several doubtful or incomplete cases in the earlier series having been replaced by later and more definite cases or by subsequent completed studies on untreated cases whose earlier records were not complete. The trends exhibited by the first series are more definitely established by the present group.

Fortuitously, the sex ratio in Groups I and II is the same, rendering the average values comparable. The average age af the Addison group is higher and the disease condition more severe (all of the patients have

died during the past year) than with those having functional failures of whom but one or two were probable incipient Addisonians. These differences are reflected in the several figures given above. The predominance of the females is certainly fortuitous, as the existing statistics indicate the reverse or, at most, a relative parity of incidence. We wish at this time to emphasize our consciousness of the limited number of data in this series, and the complete lack of warrant for any broad generalization. Only the paucity of similar reports in the literature and the necessity of considering adrenal conditions as an integral part of any general method dealing with the endocrine glands leads us to present this compilation. The rarity of the condition—less than one-half per cent in our series of cases originally selected on the basis of probable endocrinopathy—means the lapse of a considerable time before an adequate number of observations could be available. As acutely conscious as the reader, of the limitations of this

TABLE III

"VITAL CAPACITY" COMPARISONS

Observation		I	II	III
Weight	High (kgm.)	+10	+17	
	Low (kgm.)	−31	−36	
	% above normal	33	22	
	Average (kgm.)	**+10**	**+15**	
	% below normal	67	78	
	Average (kgm.)	**−21**	**−15**	
	*Total avg. (kgm.)	**−11**	**−8**	**−3**
Chest	High (cm.)	−4	+15	
	Low (cm.)	−10	−17	
	% above normal	0	33	
	Average (cm.)	–	**+8**	
	% below normal	100	67	
	Average (cm.)	**−7**	**−13**	
	*Total avg. (cm.)	**−7**	**−5**	**−2**
Lung Volume	High (cc.)	−29	± 0	
	Low (cc.)	−51	−29	
	% above normal	0	0	
	Average (cc.)	–	–	
	% below normal	100	100	
	Average (cc.)	**−47**	**−14**	
	*Total avg. (cc.)	**−47**	**−14**	–

*Weighted for number of cases.

report, we offer it as a first approximation and as indicating tendencies only and not defining limits. The ages are similar to those of the other endocrine groups. The one child (III), a girl of seven, will be discussed later in the body of the paper. The heights are in no way remarkable nor indeed are the other values determined by the bony structure. The Sitting Height-Chest Ratio exceeds that which would be determined if only women were considered, and indicates probably that degree of emaciation which subsequent comparisons disclose. Taking Dreyer's (16) figures as the best available, the normal male ratio would be 1.053, the female 1.152 or, weighting for relative representation, the normal value would be 1.119. Group I gives the value 1.184, and Group II the slightly lower value of 1.173. The weight averages are below those recorded in the other endocrine groups. The average lung capacities of Groups I and II reflect

the degree of asthenia incident to the progress of the disease. Interestingly, that for Group II compares favorably with the group averages of the other endocrine series.

As previously noted, the absolute data frequently are less informative than comparisons with so-called normal standards. Following our earlier practice these may next be considered.

Applying the comparisons with the Dreyer and West standards, as described in the earlier papers, it is obvious that while a few of the cases were overweight, the majority fell below prediction and the net average was actually 11 per cent for Group I and 8 per cent for Group II below that calculated. In passing it may be said that in our entire series of studies this gland is the only one determining a negative average. The

TABLE IV

URINE DATA

Observation		I	II	III
Volume	Average (cc.)	750	1240	480
Specific Gravity	Average	1.011	1.016	1.007
Albumin	Positive (%)	100	100	100
Casts	Positive (%)	67	44	0
Sugar	Positive (%)	67	33	0
Urobilinogen	Positive (%)	0	0	0
Salol	Average (min.)	70	79	75
Urea Curve	Normal (%)	33	*14	—
	Low (%)	67	*86	—
Phenol-Sulphone-Phthalein, 2-hour elimination	Average (%)	53	47	53

*Test not applied to two cases.

loss in predicted lung volume is of very significant magnitude in Group I but, oddly enough considering the asthenia characteristic of these cases, in Group II is somewhat less in amount than that observed with the other endocrine glands. The elimination, in this group, of obesity, an other depressing factor of predicted lung volume, may explain the observation.

Certain of the observations, where the urine was the material examined, are collected in the next table.

The individual volume and specific gravity values show fluctuations analogous to those of the other series; the average of Group I shows a lowered kidney permeability while that of Group II equates well with normal findings. The incidence of an albuminuria in 100 per cent of the cases, with casts in significant amount in one-half, offers a significant datum. Further, the presence of glysosuria in over 40 per cent of the cases raises a question that will be considered in detail under the caption of "carbohydrate tolerance." From the standpoint of differential diagnosis, the absence of "urobilinogen" is noted. Others have noted both increases and decreases in normal urine pigment, and McMann (17) has recorded a

single instance of the presence of a foreign pigment. The 'phthalein test would seem to indicate a somewhat lowered kidney permeability, but the extraneous factors influencing this test limit its authority. The provocative urea curve, on the other hand, is most suggestive and corresponds well with the other evidences of kidney disease. In comparison with the groups of the other endocrinopathies and with a large non-endocrine group (some fourteen hundred cases in all), we find that a low curve of elimination is shown in about 20 per cent as contrasted with the 80 per cent here observed. The Salol index is a high average value indicating in the present instance rather the lowered renal permeability than an impaired gastric motility. The partition analysis of urinary nitrogen offers additional information. In the earlier papers we have shown that an increase in the so-called residual nitrogen fraction is of frequent occurrence in all en-

TABLE V.

NITROGEN PARTITION

Observation	I	II	III
Total Nitrogen.....(gms.)	6.43	7.81	2.31
Urea Nitrogen.....(%)	79.5	77.6	78.8
Uric Acid Nitrogen.....(%)	1.5	2.1	3.5
Ammonia Nitrogen.....(%)	4.3	5.4	4.3
Creatinin Nitrogen.....(%)	4.5	4.7	1.4
Residual Nitrogen.....(%)	10.2	10.2	12.0
% of cases with residual = or over 9%	33	67	100

docrine and certain non-endocrine conditions. Further, one of us (18) has demonstrated that this increase is ascribable, in part, to the presence in abnormal amount of substances usually occurring in but very small quantities. In addition, however, there remains a moiety which is unaccounted for by the increase of known constituents and which patently must be referable to the presence of unknown nitrogen containing substances. We shall touch on this point again in the consideration of the blood chemistry. Several other observers have recorded either the presence of increased amounts of normal or the appearance of abnormal constituents, but the contradictory opinions seem to exist about these as well as the general protein metabolism. Our figures show an average for the series superior to the established normal, exceeded only by that for thyroid and with more than half of the cases exhibiting significant increase above normal. The percentage values of the several other constituents accord well with accepted standards. The absolute nitrogen elimination is, however, significantly low. Reference to the composite group of the other endocrinopathies already mentioned shows an average of substantially 9 grams as against the adrenal value 17 per cent lower. Since these figures were derived from a study of the urine nitrogen partition alone, and not from protein

metabolism experiments, no inference can be drawn as to retention. The patients were observed under the same conditions of liberal varied diet as were the other members of the series. That they show a characteristically lower nitrogen elimination for whatever cause, and that the partition formula departs from normality, may be regarded as indicated.

The results from the determination of certain blood constituents are given in Table VI.

TABLE VI

BLOOD CHEMISTRY

Observation	I	II	III
Non-Protein Nitrogen.....(mgm.)	42	37	34
% over 35 mgm.....	100	44	0
Urea Nitrogen.....(mgm.)	17	16	11
% over 17 mgm.....	33	22	0
Uric Acid.....(mgm.)	3.4	3.6	3.3
% =or over 4 mgm. (net)*.....	0	11	0
Creatinin.....(mgm.)	1.5	1.5	1.5
Residual Nitrogen.....(mgm.)	23.3	19.2	21.3
Sugar.....(mgm.)	86	88	†112
% under 80 mgm.....	33	22	0

*All demonstrated cases of nephritis deducted.
†Value doubtful from emotional element.

The non-protein nitrogen shows an average level distinctly in excess of the usually accepted normal, the more strikingly as the urine indicates a low level of protein metabolism. Blood urea, on the other hand, is a high normal, while blood creatinin and the average uric acid concentration is normal, the latter in spite of the presence of the several cases of nephritis. Similar findings have been recorded in experimental animals, though again a word of caution must be expressed as to the interpretation of results with the moribund subjects of acute experiments. Blood chemistry values are profoundly influenced by the fatal experimental conditions. In the work of Marshall and Davis (19) certain observations would not seem to be affected by this objection. In our own cases representing the chronic as opposed to the acute condition, the non-protein nitrogen and uric acid in many of them indicate the characteristic relations of early nephritis first reported by Chace and Myers (29). The point of greatest significance is found in the residual or undetermined fraction. The average value here far exceeds the usual normal limits assigned by convention (15 ± 2 mgm.), and is even more marked in relation to our other groups.

It will be remembered in the discussion of the urine findings that the residual nitrogen fraction was found to be increased above the normal level. It was pointed out that this condition was not peculiar to adrenal involvement (the thyroid exhibits the anomaly in even more striking degree), but was shown generally in all endocrine and a fairly large group of non-endocrine disorders. As we see it, the observation rests upon an

end result of a rather wide range of metabolic disturbances, and is, at present, wholly non-specific. That the composition of the increment is a constant either qualitatively or, in relation to individual components, quantitatively, is hardly to be conjectured. Rather it is a single observation summating a large number of individual aberrations into a seemingly common end result. Further study on the character of this fraction and the variation of the amounts of individual components, may prove to be of real diagnostic import. While the urine findings present an outward

TABLE VII

RESIDUAL NITROGEN IN BLOOD

Non-Endocrine	(500 cases)	15.2 mgm.
Pituitary	(400 cases)	15.1 "
Thyroid	(200 cases)	15.2 "
Gonad (Ovary)	(200 cases)	15.3 "

general unity, the blood in the adrenal cases offers a definite difference from the other endocrine entities. The blood of decapsulated animals has been frequently demonstrated to possess an inherent toxicity [Levin (21)]. This could arise from either of two causes, i.e., failure to remove poisonous wastes normally detoxicated by the gland, or synthesis of toxic materials as the result of disturbed metabolism resulting from ablation of the adrenals. A third alternative, lowered resistance, would not necessarily connote a change in blood composition. The present observation could be adduced to support either of the first two explanations. With our present ignorance of the complete composition of that fraction of blood nitrogen in health, it is impossible at the present time to hazard even a reasonable speculation. As Folin has emphasized, the determination of the qualitative and quantitative composition of this moiety of the blood constituents offers great possibilities, both to the physiologist and the diagnostician.

The remaining observation, that of blood sugar, is also of great interest. That hypoglycaemia occurs both in Addison's disease and with decapsulated animals, has been frequently recorded. In passing it may be said that the recording of blood sugar levels far below the convulsive threshold does not excite unlimited confidence in the actual numerical values. Low blood sugar, however, has come to have an accepted diagnostic value, and reference is frequently made to it. In the present series, the average is much lower than for any of the other endocrine groups, and in 25 per cent of the cases fell below the conventional normal lower limit of 80 milligrams.* This fact, like the incidence of glycosuria already recorded, will be considered later under the general carbohydrate tolerance.

*This statement does not take cognizance of the lower levels produced by the progressively more refined methods recently published by Benedict (22) and by Folin (23). Both writers agree that the lowest figures obtainable by a dependable method give the truest picture of the actual blood sugar level. As all of the measurements here reported were made by the well known Folin-Wu method, only standards based upon it may serve as criteria. The relative values remain unaltered.

The study of the form elements of the blood (Table VIII) yields results that in the main harmonize with current thought. While a variety of abnormalities are recorded in the literature, they are largely mutually contradictory. A secondary anaemia in the later stages and a more or less established lymphocytosis are the sole points of common agreement. The latter finding appears in our observations most strikingly in Group I; the former is missing from Group II as these cases were not in the terminal phase at the time of study. We observe a slight upward tendency of the eosinophilic elements, as has been recorded by others, although the point is one of those of debate. The picture, on the whole, is one of normality, barring the lymphocytosis and the anaemia of the Addisonians. The serological tests were uniformly negative.

TABLE VIII

BLOOD MORPHOLOGY

Observation	I	II	III
Haemoglobin.....(%)	77	87	85
Erythrocytes.....(1,000,000)	3.84	4.65	4.84
Color Index.....	1.0	0.93	0.88
Leucocytes.....(1,000)	6.9	7.9	6.3

DIFFERENTIAL COUNT

P. M. Neutrophiles.....(%)	31	59	65
% =or over 75%.....	0	11	0
Lymphocytes.....(%)	61	33	30
% =or over 33%.....	100	33	0
Eosinophiles.....(%)	2	2	5
% =or over 3% (net)*.....	33	22	100
Endothelial Leucocytes.....(%)	6	6	0

*All cases deducted which present non-endocrine causes of eosinophilia.

In the next table will be found the results of the respiratory metabolism studies and certain concomitant observations.

The general consensus of opinion would seem to indicate that adrenal failure determines a downward tendency to the basal metabolic rate. Exceptions to this have been noted,* but in the main, dependable data show decrease which in some cases, at least [Muirhead (24)] assumes a very tangible magnitude. The animal experiments recording the converse of this were in some cases, at least, not controlled for superimposed effects such as movement. Conceivably, the species also might play some part. The calorigenic action of adrenalin has been measured by Boothby and Sandiford (25) and their interpretations are confirmed by Graefe (26) in his recent monograph. This latter observation does not implicitly settle

*Boothby and Sandiford (4) in their series showed one case with a rate above +20 per cent, while nine were within the normal range, only three falling below —10 per cent.

the question, since two glands are involved, but certainly does not negative a drop in basal rate from lowered adrenal function. In our own series the values ranged from —5 per cent* to —32 per cent; the net average (12 cases) being —17 per cent. Following the general method of presentation of Boothby and Sandiford, we have 4 between ±0 and —10 per cent, 4 between —11 per cent and —20 per cent, 2 between —21 per cent and —30 per cent, and 1 below —30 per cent. As stated in the table, one case was omitted. The patient was a psychoneurotic woman, very restless and unable fully to co-operate. Several measurements were made, the best being 4 per cent above prediction but this test was unsatisfactory and the observed rate significantly above the truth. Several of the other cases were

TABLE IX

RESPIRATORY METABOLISM

Observation	I	II	III
Basal Metabolism*			
Deviation.....High.....(%)	−10	†−5	
Low.....(%)	−21	−32	
% below prediction	100	100	
Average	**−17**	**−15**	**−29**
% between +10% and −10%	0	33	
% =or below −10%	100	67	100
Temperature.....Avg.....(deg.)	**98.1**	**97.9**	**98.8**
Blood Pressure			
Systolic.....Avg.....(mm.)	**90**	‡**96**	**90**
% =or under 110 mm	100	89	100
Diastolic.....Avg.....(mm.)	**54**	‡**59**	**52**
% =or under 65 mm	100	89	100
Pulse.....Avg....(per min.)	**75**	**74**	**94**
Respiration.....Avg....(per min.)	**16**	**13**	**27**
Alveolar Carbon Dioxide.....(mm.)	**38**	**36**	**34**
% under 40 mm	100	100	100

*One case (psychoneurotic) omitted from Group II. See text.
†Febrile temperature 99.1°.
‡One case with long-standing cardio-renal disease and slight hypertension omitted.

probably not basal, and one had a slightly febrile temperature. As with the gonad cases where a similar inhibiting condition obtains, the values secured have been reported as they are representative of the results obtained with this group of patients. In the main it may be said that the severity of the condition is reflected in some measure in the degree of depression of the basal rate. This is not rigorously true, however, as the asthenia leads to a nervous instability and to restlessness.

The characteristic hypotension recorded by many others is here definitely present. The average systolic falls below 100 mm. and individual observations of less than 90 are recorded. The slightly increased pulse is not clearly displayed, but again this may be referable to the phase of the disease represented. Certainly the average indicates no downward tendency. The respiration rate confirms the conclusion offered above, as the lowered rate is observed only in the terminal phase.

*Average of comparisons with both Harris-Benedict and Aub-duBois predictions.

We did not observe the hypothermia which is said to be characteristic of the condition. A temperature of 97° F. is the lowest recorded in the series, while one is slightly above 99°.

Alveolar carbon dioxide is a low normal. This is probably more apparent than real, as the asthenia of the condition makes it difficult to secure a really representative sample. The value recorded is undoubtedly a minimum, but equally, is probably representative.

The last observation to be recorded in this portion of the report is the Carbohydrate Tolerance, (Table X).

The findings here are diametrically at odds with the usually expressed opinion on the influence of the adrenal on sugar tolerance. There is a particularly voluminous literature in this field, and all writers seem to concur in the opinion that adrenal failure produces an increase in the

TABLE X

GALACTOSE TOLERANCE

	Group	Normal	Observed	Deviation
I	Addison's Disease			
	B-133	40	5	−87%
	B-325	30	20	−33%
	B-977	40	20	−50%
				Average −53%
II	"Hypo-Adrenalism"			
	B-62	40	50	*+25%
	B-144	40	30	−25%
	B-155	30	20	−33%
	B-182	40	30	−25%
	B-323	40	20	−50%
	B-421	30	5	−83%
	B-440	40	10	−75%
	B-505	40	10	−75%
	B-567	30	10	−66%
				Average −45%
III	Pubertas Praecox	20	20	± 0

*See text.

tolerance. The great majority of the studies from which this opinion derives, are based upon the influence of epinephrin injections on the level of blood sugar or, less frequently, on the appearance of glycosuria, procedures outside the range of this discussion. Of the very few studies which correspond with the present investigation, Eppinger, Falta, and Rüdinger (27), state that they found a very high tolerance for glucose in three cases of Addison's disease. Mussio-Fournier (28), examining the urine, found a high tolerance for glucose in one atypical case, while numerous writers have reported the low blood sugar curves which are interpreted as indicative of an increased assimilation limit. In only one paper, that by Forschbach and Severin (29) in which blood sugar curves were the criterion, has the writer been able to secure any evidence of a contrary observation. In this latter paper, one case of Addison's disease is reported with glycosuria after the test meal, while this case and one other show a significant rise to the blood sugar curve. The paper as a whole, however,

does not inspire unreserved confidence in the accuracy either of the diagnoses or of the numerical data. Such sugar levels as 25 and 38 are so intrinsically improbable as to require substantiation.

In opposition to the general opinion, with but a single exception all the cases in this series showed a normal or depressed tolerance for galactose. Question as to diagnosis is answered by the fact that the low tolerances were exhibited by the subjects presenting the typical Addisonian syndrome subsequently verified at autopsy. The one subject showing a slightly raised tolerance (+25 per cent) had an advanced nephritic condition of long standing to which the anomalous finding might be attributable. That an apparent kidney disorder is frequently found in adrenal disease, the data of this series amply testify. The contradictory results of the other observers already cited may be due to a lessened kidney permeability, possibly to the fact that glucose and not galactose was the sugar exhibited, or equally to other and unknown causes. The frequently reported hypoglycaemia of adrenal failure has been confirmed in this series. It is possible that this might influence the so-called tolerance if the latter were determined solely by the shape of the blood sugar curve without observation of the urine changes. Sugar anomalies produced by epinephrin injection fall outside the scope of the present discussion, as presumably they involve a mechanism different from that operated by the simple oral administration of a dose of sugar. Confirming our findings in this matter is the independent observation earlier recorded of an incidence of glycosuria in nearly one-half of the cases in the series. When one remembers the blood sugar levels recorded, it is evident that something intrinsic in the condition has affected the entire carbohydrate metabolism and that to the end result of lessening the power of the organism to utilize sugar. Parenthetically, the glycosurias noted above do not have to invoke the influence of a relatively foreign sugar for an explanation.

Patently, much more work must be done on a larger number of authentic cases to permit final judgment in the matter. As it now stands, we have observed, in a few definite cases of adrenal disease, a depression of the tolerance for galactose which assumes, as the table indicates, a magnitude almost equal to that conditioned by pituitary aberration. In conclusion it may be said that the well known hyperglycaemic action of suprarenin injection may to some extent have influenced thought. If we regard our cases as of adrenal failure, our findings superficially, at least, are contrary to natural prediction. The dualistic nature of the gland may account for the findings. With our meager data we are unprepared, at this time, to do more than offer our findings as facts without further effort to explain existing seeming contradictions.

PART II

The clinical analysis of this small group of cases presents some difficulties. The child (Case C-16) is omitted entirely since her case is not

comparable to any of the others. A full protocol with discussion will be given later in the paper. Of the remaining twelve, three were clear-cut demonstrated cases of Addison's disease with pigmentation, six were seemingly functional failures with half of them possibly incipient Addisonians, and the remaining three were of an even more doubtful adrenal etiology. As, in the main, they have conformed to the general picture defined by the more authentic cases, and further, as thorough study failed to disclose any other cause for their presenting difficulties we have felt warranted in their inclusion.

The authors desire to repeat, perhaps redundantly, that they are acutely conscious of the short-comings of this series. Only the Addisonians are certainly cases of adrenal disease and they are but three in number. Their several pictures are consistent in detail, however, and may be adopted as criteria for the discussion of the larger number of assumed functional cases. Consideration of these latter is felt to be permissible in view of the many serious observers who avoid a guileless acceptance of the more extreme synthetic correlations of speculative endocrinology and yet concede the possibility of a lowered functional activity of the adrenal glands. The existence of accessory medullary and cortical tissue in other portions of the body with the possibility of local involvement, offers additional ground for conceiving such a condition to be possible.

One other point should be noted. With so brief a series as the present, statistical analysis is not highly significant. Agreement with the results of the more extensive surveys of others offers some slight support for the possible accuracy of the diagnosis; difference emphasizes only the limited amount of our material.

Without further preamble, we may undertake a brief clinical analysis of the cases.

The sex incidence of the disease is usually stated as equal or with a slightly greater frequency among females. In the subdivisions of the present series, the females are twice the number of males.

The ages can be presented in tabular form.

TABLE XI

AGE AND ONSET

Decade	*Number*
21-30	6
31-40	2
41-50	2
51-60	0
61-	2

On the whole these values are in harmony with the usual record which places the years from 20 to 40 as those of greatest frequency. Late cases are known, however, the disease having appeared after the age of

80 in a few of those reported. Our three Addisonians were respectively 32, 48, and 61 years of age.

The time of onset in these three cases varied from three to twelve months before admission to the Clinic, with an average of nine months. As all of them have since died, the duration of the disease is known. Subject B-133, the youngest, had been sick for about one year at the time of admission and died almost exactly three years later (see Protocol in Part III). Subject B-977 exhibited an acute condition which began three months before our contact and ended three months later. The third Addisonian had been ill for one year prior to admission and lived for three years and one month after our study.

Of the functional group, five had been ill for less than four years, and one each reported severally 5, 10, and 25 years' duration. The last of these, subject B-323, referred her condition to some trauma to the coccygeal region at that time.

The family histories were particularly irrelevant, only one patient reporting tuberculosis, and one malignant neoplasm in fairly close relatives. Two others reported diabetes, the only endocrine condition cited, in reasonably near relatives.

The previous illnesses can be presented best in tabular form.

TABLE XII

PREVIOUS DISEASES

Measles	11	92%
Whooping Cough	8	67%
Mumps	7	59%
Chicken-pox	7	59%
Influenza	5	42%
Pneumonia	2	17%
Trauma to Coccyx	2	17%

While none of the Addisonians had a previous history of tuberculosis, three of the functional group had positive histories of earlier involvement, and in two of the others it was probable although no active process could be demonstrated at the time of study.

Two of the patients in the second (functional) group had a history of some trauma to the coccygeal region, possibly significant in view of the accessory tissue normally found there.

Seven of the twelve had had one or more tonsillectomies, a proportion in accord with the incidence of tonsil diease already noted in the other endocrinopathies.

The chief complaints, as presented by the patients, are instructive.

Asthenia was offered as a major difficulty by eleven, and the twelfth case gave it as a minor symptom. The three patients with Addison's dis-

ease all complained of their pigmentation, and four of the functional group exhibited pigment changes of lesser magnitude in the skin.

Five of the group reported nervous instability as a principal symptom, and all of them exhibited it in significant degree.

TABLE XIII

CHIEF COMPLAINTS

Asthenia	11
Pigmentation	3
Nervous Instability	5
Gastro-Intestinal Disorders	3
Pain	4

In this connection, a few words may be apposite in regard to the personality changes engendered by this disease. Analogous alterations have already been commented on in our papers on the thyroid and the gonads. While a psychical asthenia accompanies the physical fatigability, it does not determine an apathy in environmental reaction. Sufferers from Addison's disease are highly emotional, irritable, and the victims of apprehensions and needless worries. Perspective is lost on the affairs of life, and annoying or disconcerting trifles assume the magnitude of major calamities. Mental depression is noted much more frequently than the reverse. They differentiate, however, from the sullen truculency of the hypothyroid subject and the shrill self-insistence of victims of gonad failure.

Gastro-intestinal disorders were of primary importance to two, and in addition, six more complained of poor appetite, flatulency, and other evidences of impaired function. Five were constipated, and one had persistent diarrhoea.

Pain was a common finding and in four assumed major importance. It was rarely delimited as to site, but was usually found in the abdomen in every case as well as in other portions of the body.

The asthenia, pigmentation, and gastro-intestinal symptoms are frequently referred to as the triad of cardinal symtoms, while the other two are of usual occurrence. The frequency of representation of them in this group lends some support for the diagnosis in the assumed functional cases. While they may all derive from numerous other causes, some of these latter had been excluded by other parts of the study. Further, the symptom complex was but one evidence among the many, by the integration of which the diagnosis was established. We have already emphasized the necessity of regarding each diagnostic factor as significant only in its correlation with the general picture made up of many other independent measurements and observations. The agreement of our findings with those generally accepted as significant of adrenal disease, does not establish

a diagnosis but adds supporting evidence to the possible accuracy of our interpretation.

The majority of the patients showed an excessive susceptibility to infections of the respiratory tract, as shown by the data already recorded and by the fact that half of them reported very frequent colds (4), coryza (4), sore-throats (5), and kindred conditions.

Several of the group were subject to vertigo, and a number gave a history of fainting spells. Five complained of frequent and severe headache. Several had had otitis media in earlier years, and two showed a definite impairment of hearing. Nocturia was noted in 50 per cent, and intermittent polyuria in two patients. In the previous section the objective evidences of kidney involvement has already been emphasized. A true nephritis would seem to be even more frequently an accompaniment of adrenal disease than is the lowered permeability simulating nephritis of the thyroid failure.

The menstrual history of the eight women shows a relative normality.

TABLE XIV

MENSTRUATION

	Amount		
	Increased	*Normal*	*Diminished*
Irregular 3	1	0	2
Regular 5	0	4	1
Total.....	1	4	3

All of those showing irregularity had an increase in the interval, and with those of the entire group where the flow was not normal, the tendency was toward diminution. This is in harmony with the usual record of lowered exocrine activity of the gonads in adrenal disease.

A second supporting, if indirect, evidence is found in the marital histories of the group.

Only three of the twelve were married, two women respectively five and seven years, and one man whose married life extended over nearly forty years. Each of these unions had been productive of but one child, and there was no history of miscarriages. The direct data on libido were too meager to be significant, but the record given above may be regarded as possibly suggestive. In all of the other endocrine groups, including that of the gonad failures, the percentage of marriages is very much greater.

The physical examination yielded relatively few significant data.

Loss of weight and emaciation are usually predicated for adrenal disease. Three of our twelve patients were above their predicted weight, and of these one was the Addisonian in whom the disease ran a rapid course. This latter fact probably accounts for the anomaly. She was

underweight at the time of her death. The remaining nine were all below their predicted weights although three of them were still within the conventional normal limit of —10 per cent. The six remaining subjects averaged 22 per cent below their normal weight, and one of these (not an Addisonian) was 36 per cent below the calculated normal.

As has been noted above, 59 per cent of the group were pigmented in a greater or less degree. Several of the remainder were sallow, and only one exhibited a really healthy color of the skin. This was the patient (Case B-144) who was one of the doubtful group.

The hair presented nothing remarkable, there being no instance of a recognized deepening of color or marked anomaly in amount or distribution. Five of the patients had frankly poor teeth, and the dentition of several others was in but fair condition. As already noted, some patients had had tonsil operations, the tonsils of the remainder were normal.

One female patient had a slight thyroid enlargement; at the time of examination none exhibited adenopathy though several had an earlier history of enlarged glands. Four patients gave evidence of past or present pulmonary disease, and three showed abdominal tenderness. Five exhibited diminished reflexes. The remaining features of the examinations were not substantially significant.

Of the special examinations but few excite comment. Four of the patients gave evidence of apparently earlier pulmonary disease and the pyelograms of two of the Addisonians showed destruction in the upper portion of the kidney.

The eye examination demonstrated 75 per cent to have enlarged blind spots, but only 25 per cent showed yellowish discs. In only one case was there a significant contraction of the fields, and this was in one eye, the patient suffering from iritis in the other.

Neurological examinations confirmed the findings of the routine report, while none of the other observations threw light on the potential endocrine condition.

In the main it may be said that the members of the functional group gave pictures varying in degree rather than in kind of involvement from those of the Addisonians. As has been noted, the three established cases of Addison's disease differed from each other in certain respects, as one would naturally anticipate, and the majority of the functional cases showed no greater variation from conventional standards. No attempt has been made to review the literature as the few points of note in the clinical picture of this rare condition are matters of too general agreement to require debate.

Following the practice of the earlier papers in this series, the next section will be devoted to presenting the individual details of certain of the more representative and interesting cases in the form of protocols.

Part III.

Case Protocols

The significant laboratory data of the first group are given in tabular form.

TABLE XV.

Addison's Disease

Observation				
Case Number		B-133		B-977
Date	Jan., 1924	Feb., 1924	May, 1924	April, 1928
Interval (mos.)	–	1	3	–
Sex	F	F	F	F
Age (yrs.)	32	32	32	48
Height (cm.)	162	162	162	158
Weight (kgm.)	51.8	50.2	50.0	61.4
Weight Deviation (%)	−8	−11	−11	+10
Lung Volume Deviation (%)	−28	−29	−28	−42
Basal Rate Deviation (%)	−6	−10	−13	−21
Blood Pressure (mm.)	104/62	90/54	108/70	90/58
Pulse (per min.)	94	74	76	86
Temperature (deg. F.)	97.2	98.4	97.6	97.1
Alveolar CO_2 (mm.)	31	35	36	40
Urine Volume (cc.)	2150	730	1800	720
Specific Gravity	1.013	1.025	1.015	1.014
Albumin	+	+	0	+
Casts	0	+	0	+
Sugar	0	+	0	0
Total Nitrogen (gms.)	13.58	8.37	15.13	6.13
Residual Nitrogen (%)	2.4	7.1	11.2	7.2
P. S. P. 2-hour Elimination (%)	79	62	–	42
Non-Protein Nitrogen (mgm.)	40	39	42	43
Uric Acid (mgm.)	4.3	3.4	4.2	3.5
Sugar (mgm.)	80	75	80	99
Haemoglobin (%)	90	85	90	75
Erythrocytes (1,000,000)	5.52	4.28	4.61	3.81
Color Index	0.82	0.99	0.98	0.98
Leucocytes (1,000)	8.2	8.7	6.8	8.3
Neutrophiles (%)	45	17	33	39
Lymphocytes (%)	42	73	59	50
Eosinophiles (%)	1	4	2	3
Endothelials (%)	12	6	6	8
Misc. (%)	0	0	0	0
Galactose. Normal (gms.)	40	40	40	40
Observed (gms.)	–	5	–	20
Deviation (%)	–	−87	–	−50

Group I. Addison's Disease.

CASE B-133. (Chronic) The patient's chief complaint was of pigmentation of the skin coupled with a marked asthenia. Since early childhood, she had presented several dark brownish moles on the face and a large irregular naevus-like dark pigmented area on the lower anterior half of the left side of the neck. Two years previously she noted an increase in the number of moles on her face, and one year previously a general darkening of the skin, most pronounced on the face, hands, and a band surrounding the middle of the body. The asthenia she dated from an attack of the grippe about a year previously, so that the pigmentation and weakness showed substantially the same chronology.

Family History: **The father died at the age of 38 of diabetes. There were three living sisters and three others who had died in childhood of acute infections.**

Past History: The patient reported the minor ailments of childhood, tonsillitis every year until a tonsillectomy six years earlier, and in addition, the attack of grippe already mentioned. She had had no association of which she was aware with tuberculosis. The other significant points in the history were abscessed ears ten years previously, teeth requiring much dental attention, and an occasional gastro-intestinal disturbance characterized by flatulency, distress, and nausea. She had had occasional fainting spells, and at times numbness and tingling in the hands. The patient was unmarried, established the catamenia at the age of 14, and gave an entirely normal menstrual history.

Physical Examination: She was a fairly well developed, poorly nourished woman, 32 years of age. The exposed surfaces showed a peculiar copper colored appearance which during the examination was also observed in a broad irregular girdle about the waist. The other portions of the body were also brownish but less strongly pigmented. The naevus on the neck was remarked, and numerous brown moles on face, neck, and arms. The lips were somewhat pigmented, as were the gums and small areas of the buccal mucosa. Examination of the lungs showed a questionable increase in intensity of the breath sounds at the left apex, and a few dry rales heard throughout both lungs. There was slight tenderness in both costal vertebral angles, a fine tremor of the hands, and a bluish color of the nails. No evidence of cardiovascular disease was detected.

Laboratory Summary: The urine volume was somewhat high; there was a trace af albumin. The elimation was excellent, the protein intake ample, and the partition formula normal. The blood morphology was normal except for a marked lymphocytosis. The blood showed an increase above the normal of all of the nitrogenous constituents, and a blood sugar at the low level of the normal. The vital capacity measurements showed the patient to be 8 per cent underweight, and with a significant loss from the predicted lung volume. The basal rate was recorded as —6 per cent, with low blood pressure, rapid pulse, and slightly sub-normal temperature. This value of the basal rate was not regarded as accurate since the patient was slightly nervous.

Radiography of the chest give normal findings, but an indefinite shadow was remarked above the upper pole of the left kidney.

Skin Examination: The observer at this time commented on the suggestion of Addison's disease, felt that mineral poisons and a chloasma of toxic origin must also be considered, and recommended a biopsy.

Discussion: Feeling that the observations available were too limited to warrant a final diagnosis, and desiring to study the patient more thoroughly in the hope of resolving the condition, she was admitted to the Hospital a few weeks later and a much more complete study was undertaken. The interval history was irrelevant.

Second Examination: The urine volumes were found to be somewhat low, and the urine contained albumin, sugar, and granular casts. Her protein intake had decreased although it was still above a maintenance level. The residual nitrogen fraction showed a definite upward tendency although still within the conventional normal limit. The blood showed a marked increase in the lymphocytes and a 4 per cent eosinophilia. There was evidence, for the first time, of a slight degree of anaemia, with a color index of one. The blood chemistry values were somewhat lower for the uric acid, the high non-protein nitrogen remained unchanged, while the blood sugar had sunk below the conventional normal limit. The 'phthalein test, though still normal, had fallen off somewhat. The patient had lost 1.6 kgm. weight. The lung capacity was substantially unchanged. The basal rate was 10 per cent below prediction, and again the measurement of the observed rate was undoubtedly somewhat above the truth. A sugar tolerance test was performed with galactose, and it was found that the assimilation limit was greatly depressed, even so small a dosage as 5 grams being enough to produce a transitory appearance of galactose in the urine. The alveolar carbon dioxide was still low, an observation ascribed in part to the patient's weakness, with consequent difficulty in collecting a representative sample.

Neurological Examination gave entirely normal findings throughout.

Pelvic Examination gave normal findings.

Radiography: The skull and sella were normal. An area of calcification in the falx cerebri was reported. The chest was negative, and the radiogram of the abdomen failed to confirm the shadow near the kidney which had been

previously recorded. Some density of the right mastoid cells was noted, the sinuses were otherwise normal.

Eye Examination: The discs were yellowish in color, the blind spots slightly enlarged; the remaining findings were normal.

Urea Curve: The data showed a depressed elimination, both qualitatively and quantitatively.

Biopsy: A biopsy was performed and the excised tissue was subjected to careful examination by Dr. A. M. Greenwood. The portion from the naevus was reported by him as characteristic of the tissue from which it was taken. The second section, which was excised from another part of the neck, showed only increased pigment in the basal layer, which, with special staining, was demonstrated to be melanin.

Discussion: The patient's history and her presenting symptoms were naturally suggestive of Addison's disease. There were further in the literature a few records of lowered basal rate in this condition in man, perhaps the most significant of which were the records of Muirhead (24) from the Mayo Clinic, and those of Aub (30) and his associates. The reports from several laboratories of increased basal rate in experimental animals with injury to these glands was not regarded as significant since the animals were not in a basal state. On the other hand the injection of adrenalin is known to increase the respiratory metabolism. The patient's sugar tolerance represented a sharp divergence from the few existing records in the literature. This has already been discussed earlier in the paper. The patient presented evidence of lowered kidney permeability, the low blood pressure and blood sugar generally associated with Addison's disease; certain of the other possibilities such as primary anaemia and bronzed diabetes were practically eliminated by certain of the other observations. On this basis a tentative diagnosis of Addison's disease was established and medication instituted.

The clinical features of particular interest were the absence of demonstrable foci of tuberculosis elsewhere in the body, the albumin and casts in the urine, the evidences of depressed renal function furnished by the blood chemistry, phenolsulphonphthalein test, and urea curve, and the character of the asthenia.

The impression still persists that non-pulmonary tuberculosis is practically always associated with the pulmonary form, and that a diagnosis of non-pulmonary tuberculosis rests on insufficient evidence if the former is not demonstrable. While it is true that autopsy usually shows some evidence of pulmonary involvement in those patients exhibiting the disease elsewhere, it is more often than not impossible to demonstrate the association clinically. Therefore absence of pulmonary tuberculosis demonstrable by clinical methods should not deter one from making the diagnosis of the disease elsewhere in the body.

Albumin and casts were present in the urine of the majority of our patients with Addison's disease, and were generally accompanied by other evidences of disturbed renal function. (See table XV.) Such findings, generally significant of nephritis, should not be allowed to direct one's attention away from possible adrenal disease if they are accompanied by significant hypotension and asthenia of the characteristic type. If pigmentation is present there is little danger of this, but if there is no pigmentation, as happens, according to Falta (9), in nearly one-third of the cases, undue emphasis upon the urinary findings may decoy one away from the true diagnosis.

The character of the asthenia in our patients with Addison's disease has been so typical that its main features seem worth emphasizing. Although there is usually complaint of constant lack of energy, the feature peculiar to adrenal destruction has been the sharp exacerbation of weakness upon effort and its rather rapid remission when effort ceases. The patient under discussion furnished a clear example. She was a school teacher and was able to carry out most of her tasks without distress, although she was very weary when the day's work was over. An attempt to lead the class in a short and easy "setting up drill," however, would almost always produce a feeling of profound weakness, accompanied by dyspnoea, trembling, and frequently nausea. Ten or fifteen minutes rest would result in complete disappearance of this asthenic condition, leaving her "practically as good as she was before." This cycle of events which seems to lend supporting evidence to Cannon's emergency theory is, in our experience, typical of Addison's disease (if severe cardiac disease be excluded), and is of fundamental importance in distinguishing it clinically from other conditions causing asthenia.

In April the patient returned for a basal metabolism test which showed a level of —5 per cent under what seemed to be satisfactory conditions. The blood pressure had risen to 112, and the patient apparently was much improved. In May a series of observations was made (see table) which may be briefly reviewed.

The urine was again ample in volume, as in the beginning; albumin, sugar and casts had disappeared; the elimination was excellent. The appetite had improved, and the protein intake was almost double that of February. The residual nitrogen, however, had increased to a point significantly above the conventional normal. The blood still showed a marked lymphocytosis but definitely lower than that recorded in February, while the eosinophilia had returned to a normal value. Both the red count and the haemoglobin were somewhat increased, and there was no secondary anaemia. The blood sugar showed an increase to the initial low normal level. The nitrogenous constituents, however, had also increased to substantially their initial value. The patient's increased protein intake undoubtedly contributed something to this. The weight was substantially unchanged, as was the vital capacity. The basal rate was now 13 per cent below prediction, with the blood pressure slightly above that of the first record and significantly superior to that of the second.

Radiography: An x-ray plate taken at this time raised a question of a possible area of increased density in the mid-portion of the right wing of the sacrum.

The patient was continued under medication throughout the summer, and in the fall resumed her occupation which she had earlier been obliged to discontinue. She had gained three kilograms in weight. The blood pressure maintained the advantage shown, and her general condition showed a definite improvement.

The Muirhead treatment, modified as symptoms indicated, had been faithfully followed. But the patient was extremely sensitive to adrenalin, and its administration was omitted early since it seemed to do more harm than good. Cortical substance was, however, well tolerated, and the subjective symptoms became much less marked during its use. The patient carried on her work as a teacher with very little discomfort, and her "setting up drill" now rarely caused more than moderate fatigue. From time to time she had sudden attacks of abdominal pain and nausea, rarely causing vomiting, but on the whole her condition was excellent and her energy sufficient.

During the Christmas holidays of 1927 she caught cold. In spite of it she returned to work two days later. She showed no untoward effects from the "cold" when she started for school in the morning, but on reaching home in the afternoon she complained of the abdominal pain previously mentioned, and of difficulty in breathing. Her physician was summoned and found her in a state closely simulating surgical shock. The extremities were cold; pulse small, rapid, and feeble; breathing rapid, shallow and labored. No evidence of pneumonia could be found. She grew worse very rapidly. The breathing was described by her physician as being "like that of an over-etherized patient," and it soon became necessary to hold the jaw forward to prevent strangulation. She became unconscious and died, apparently of respiratory failure, within eight hours after returning to her home, on foot.

We were fortunate in securing an autopsy and are indebted to Dr. Charles F. Branch for his skillful services in this connection. The skin over the entire body was of a peculiar dark brownish tinge, the lungs were normal except for a well defined edema, the liver gave evidence of recent parenchymatous degeneration, and the right ovary showed two small simple cysts on the upper surface.

Kidneys: Left: The approximate weight was 150 gms., it was firm, smooth, regular, and bright reddish-brown in color. The cut surface disclosed a normal relationship between the pyramids and cortex, the latter measuring about 6 mm. in width, the entire surface being markedly injected, and upon scraping yielding a slightly blood-tinged purulent material on the knife edge. The capsule stripped with ease, leaving a markedly injected surface. The pelvic epithelium was not injected. *Right:* Was similar in every respect to its fellow on the left. *Microscopic Examination:* Many of the tubules were completely desquamated, while in others the epithelium was swollen and coarsely granular; the cytoplasm and nucleus took a uniform pink stain. The lumens contained varying amounts of coagulated serum, epithelium and debris. The glomeruli were engorged and stained poorly. The vessels throughout were engorged; there was moderate general increase of connective tissue throughout which in places was infiltrated with, and showed accumulations of leucocytes. Occasional

sclerosed glomeruli were noted. The connective tissue about the pelvis was edematous.

Adrenals: After diligent search in the region where the adrenals should have been, on either side was discovered some small compact masses of pale white tissue, seemingly fibrous in character, which were preserved as sclerosed adrenals. Upon examining the cut surfaces of these masses absolutely no evidence of any structure resembling adrenals was observed. *Microscopic Examination:* Absent on either side and apparently replaced by a mass of tissue which upon microscopical examination appeared to be enlarged sympathetic ganglia.

From the clinical standpoint the most interesting features of this case are the long duration of the disease after the diagnosis was established and the considerable improvement under treatment, which is astonishing in the light of the autopsy findings, and the character and brevity of the final stage, suggesting that a very small fraction of the total adrenal tissue may be sufficient to support life, but that even a mild infection may overwhelm the patient.

CASE B-977 (ACUTE). The patient's chief complaint was of a brown coloration of the skin, coupled with a marked degree of asthenia. Three months previously the patient's mother had died, the event producing a profound emotional shock. Following this she became very weak and began to lose weight rapidly. A few weeks later she found herself unable to continue her employment. She developed an attack of grippe, and during her convalescence noted that her skin was becoming brownish in color. During the three months of the course of her complaint she had lost 25 lbs. The weakness and pigmentation had both been progressive. Five days before admission she had had a single attack of vomiting without well defined cause.

Family History: The mother died following an operation for hernia at the age of 75, and the father at the same age of cerebral hemorrhage. The remaining family history was entirely irrelevant.

Past History: Beyond measles at three, diphtheria at 13, and a tonsil operation at 38, the patient's history was relatively uneventful. She had always been healthy and a steady worker. Her teeth had been removed for pyorrhea. She stated that a year and a half previously, after an attack of epigastric pain, a diagnosis was made of duodenal ulcer, and under medical advice she had been on a bland diet since that time. The menstrual history was entirely normal up to six months ago, but in this interval she had missed three periods. As the patient was 48 years of age she ascribed this to an approaching menopause. She reported a slight tingling sensation in the right hand occasionally, and a slight skin eruption on the arms after eating tomatoes. There had been no association with tuberculosis.

Physical Examination: The patient was a well-developed, well-nourished woman of 48. There was a bluish-brown pigmentation all over the body, most marked on the exposed surfaces. The patient was apathetic and appeared fatigued. There was apparently some loss of hearing in both ears. The buccal mucosa was pigmented, the chest apparently normal, the radial arteries were slightly firm. Routine neurological findings were substantially normal except for somewhat poor pass pointing.

Laboratory Summary: The urine was somewhat scanty and it contained albumin and a very few hyaline casts. The elimination was poor. The protein intake was below a maintenance level, and the residual nitrogen showed an upward tendency although within the conventional normal limit. The blood morphology showed a lowering of both haemoglobin and leucocytes, and a normal color index. There was a marked lymphocytosis and a 3 per cent eosinophilia. The blood non-protein and urea nitrogen values are definitely above the normal level, while the blood sugar was normal. The 'phthalein output was definitely low, and the urea index below the normal. The patient was 10 per cent overweight but nearly 50 per cent below her predicted lung volume, a finding probably referable to her asthenia. The basal rate was 12 per cent below prediction, with definitely low blood pressure, and, at the time of the test, a somewhat rapid pulse. Later evidences seemed to indicate that the basal rate, as recorded, was probably distinctly above the truth, and that the real rate was between 20 per cent and 30 per cent below prediction. The value recorded in the table, derived from a second test, was —21 per cent, and this was still probably somewhat high. The patient's sugar tolerance was half the normal level.

Chest Examination gave no evidence of disease.

Endermal Skin Tests gave no evidence of protein sensitivity.

Liver Function (*McClure*) determination indicated normal biliary function.

Orthopedic Examination: Moderately pronated feet were the only abnormality recorded.

Skin Examination: The appearance was regarded by the examiner as typical of Addison's disease.

Radiography: A series of gastro-intestinal plates showed a constant defect consistent with duodenal ulcer. There was some degree of visceroptosis. The skull and sella were normal, heart and lungs normal, and a plate of the lower leg where the patient had a tender spot showed no abnormality.

Cardiogram gave normal findings except for a relatively low voltage consistent with the patient's adynamic state.

Audiogram showed normal hearing.

Cystoscopic Examination gave normal findings.

Eye Examination: The discs were yellow and the fundi showed slight vascular sclerosis and a generalized tessellated pigmentation.

Urea Curve: Was normal in shape and gave evidence of good elimination.

Levulose Tolerance was much depressed.

Icteric Index and Van den Bergh reactions indicated normal function.

Pyelograms: The right renal pelvis was dilated; the calyces blunted. The left kidney was of the spider type.

Discussion: The whole general picture here was felt to be consistent with Addison's disease in a somewhat acute state. The lowered sugar tolerance, while not in accord with other reports in the literature, was consistent with our own observations. The Muirhead treatment was initiated, the patient remaining under observation in the Hospital. One month after beginning treatment a satisfactory basal rate showed a level only 4 per cent below prediction, with distinctly low blood pressure (88/52) and a slightly rapid pulse. The patient's condition did not improve, however; the asthenia was progressive and complicated by sensations of pain which were not exactly localized but seemed to be confined to the body. Toward the end of the second month the patient's failure became more rapid, and early in the third month after admission, death supervened. An autopsy, the details of which we owe to the courtesy of Dr. Charles F. Branch, showed bilateral pulmonary tuberculosis and Addison's disease.

Adrenals: The left weighed 24 grams. It was slightly injected and had a distinctly firm, woody feel, was coarsely nodular and the surface, instead of showing the customary fine mottling of the cortex, was almost a uniform dull, pale yellow. The surface showed no normal landmarks remaining, the cortex and the medulla being completely absorbed in a coarsely mottled, yellow and reddish gray mass, with not infrequent small islands of calcification present. No caseous material was observed, per se, although many areas simulating it were seen with the naked eye. The adrenal of the opposite side was similar in every respect to its fellow on the left. *Microscopic Examination* showed that the normal histological architecture of the organ had been completely replaced by a mass of amorphous, caseous material. This was surrounded by a thick fibrous capsule, infiltrated with a large numbers of endothelial cells and lymphocytes.

Except to emphasize its similarity to the previous case, there is little to add from the clinical point of view. The picture of impaired renal function was similar to that already discussed. The bilateral pulmonary tuberculosis was obsolete, and gave no evidence of its presence by either roentgenologic or clinical methods of examination, supporting our previous statement that inability to demonstrate pulmonary tuberculosis during life is not an argument against the existence of a non-pulmonary infection.

CASE B-421. The patient was a young man whose chief complaint was of constant glycosuria for the past five years, associated during the same interval with intermittent periods of profound fatigability. He was disposed to date the initial onset of his condition from an attack of influenza nearly 7 years previously, following which he had an attack of severe mental depression and a gen-

eral slowing up of psychomotor activity. The condition passed in a few weeks but had recurred at intervals. Five years ago, following one of them, he consulted a physician who found several per cent of sugar in the urine. A diabetic diet improved his general physical condition but did not render him sugar free. Three years ago he entered a hospital and was put on a starvation diet for six weeks with a resulting loss of 40 pounds in weight, but again without rendering him sugar free. Throughout his entire period the attacks of mental and physical depression had recurred, usually lasting from one to two months and with a gradual recovery.

TABLE XVI

"HYPOADRENALISM"

GROUP II. "HYPOADRENALISM"

Case Number	B-421	B-182	B-323	B-505	B-567	B-940
Sex	M	F	F	F	M	F
Age (yrs.)	22	22	40	26	25	68
Height (cm.)	175	163	165.5	154.5	165.5	160.5
Weight (kgm.)	64.1	34.8	60.6	41.8	52.0	51.8
Weight Deviation (%)	−6	−36	−1	−12	−3	−2
Lung Volume Deviation (%)	−8	−29	−2	−28	−15	−45
Basal Rate Deviation (%)	−32	−18	−18	*−11	−16	+5
Blood Pressure (mm.)	114/72	92/54	90/50	88/58	85/66	108/62
Pulse (per min.)	64	73	54	88	76	87
Temperature (deg. F.)	98.0	98.6	97.2	98.0	97.4	97.0
Alveolar CO_2 (mm.)	39	34	39	39	37	42
Urine Volume (cc.)	1450	1680	1050	540	610	400
Specific Gravity	1.039	1.005	1.013	1.025	1.020	1.020
Albumin	+	+	+	+	+	+
Casts	+	0	+	+	+	+
Sugar	30	0	0	0	+	+
Total Nitrogen (gms.)	14.73	4.24	7.29	6.02	5.70	4.92
Residual Nitrogen (%)	11.0	5.7	13.3	10.1	18.0	13.8
P. S. P. 2 hours (%)	61	26	48	35	55	26
Non-Protein Nitrogen (mgm.)	47	36	35	35	26	41
Uric Acid (mgm.)	4.8	2.9	3.6	3.3	2.0	5.3
Sugar (mgm.)	85	93	93	76	85	111
Galactose Normal (gms.)	30	40	40	40	30	30
Observed (gms.)	10	30	20	†20	10	20
Deviation (%)	−67	−25	−50	−50	−67	−33
Haemoglobin (%)	100	95	70	70	80	75
Erythrocytes (1,000,000)	5.36	5.12	4.21	3.55	4.02	4.40
Color Index	.93	.93	.82	.99	1.00	.85
Leucocytes (1,000)	9.3	5.9	6.7	8.4	10.8	19.2
Neutrophiles (%)	58	58	75	62	58	82
Lymphocytes (%)	28	32	24	29	37	8
Eosinophiles (%)	3	0	1	2	2	0
Endothelials (%)	10	10	0	7	3	10
Misc. (%)	1	0	0	0	0	0

*True rate lower.
†Test incomplete. Tolerance possibly lower.

Family History: The mother had a renal disorder which had led to three therapeutic abortions after she had borne four children, of whom the patient was the third. All of the siblings had died in early infancy. Cases of tuberculosis, cancer, and diabetes were recorded in grandparents and great grandparents; none in the immediate generations.

Past History: The patient's birth history showed a normal delivery but a very long labor. Development was entirely normal. At the age of six he had measles, and this was followed by an abscess in the neck and what was said to be a spot in the lungs. The chest condition apparently cleared up in about two years. He further reported minor ailments, diphtheria at the age of nine, and a severe attack of influenza at 15 with a very slow convalescence. He grew very rapidly between the ages of 13 and 15. He also had a tonsillectomy at 14, and trauma to the head at the age of 8 which apparently produced only surface injury. The regional history showed frequent earaches in childhood, soft teeth requiring much dental attention, constipation, but was otherwise not remarkable. There was a history of a fairly active sex life with no venereal infection.

Physical Examination: The patient was a well developed and fairly well nourished young man of 22. His teeth showed much dental attention, the chest was normal; there was a slight tremor of the fingers, rather abundant hair growth of normal distribution, and somewhat hyperactive knee jerks.

Laboratory Summary: The urine volume was normal, elimination and balance good. An average content of 30 grams of glucose was reported; the remaining findings were normal. The nitrogen partition determination showed an adequate protein intake and a high residual nitrogen fraction; the blood morphology was substantially normal; there was a marked increase in the level of the nitrogenous constituents, and a low normal blood sugar. The 'phthalein test and alveolar CO_2 were normal. The patient was 6 per cent underweight and of substantially normal lung capacity. The basal rate was 32 per cent below prediction, with normal blood pressure and slightly low pulse.

Adrenalin Test: Injection of adrenalin produced a definite increase in the blood sugar level from 82 to 122 mgm. with a gradual subsidence, the level being 100 mgm. at the end of two hours. There was a progressive leakage of sugar through the kidney.

Radiography: The skull and sella were entirely normal.

Neurological Examination: There was no evidence of organic nervous lesion. The examiner remarked that the pupils were widely dilated, and that after light stimulus there was a slight contraction followed by immediate dilatation.

Audiogram: Definite loss of hearing, except in the higher register was noted.

Eye Examination: The blind spots were slightly enlarged. The findings were otherwise normal, the examiner failing to confirm the anomalous pupillary reaction noted above.

Discussion: The general picture here presented was in some measure consistent with a disturbance of each of two independent endocrine glands, namely, the adrenal and the pituitary. The basal rate was of the order of adrenal or thyroid failure, but the latter is practically excluded by the patient's sugar tests since no other evidence presented of any additional cause for his depressed tolerance. In hyperpituitary cases, hypertension, and evidences of hypertensive nephritis are not infrequently found, but they are associated with an overactivity of both lobes. While most adrenal cases present a markedly lowered blood pressure, we have seen one case with an associated kidney involvement which exhibited a hypertensive level. On the basis of the markedly lowered sugar tolerance, the definitely lowered basal rate, the suggestion of renal disturbance conveyed by the picture of the blood chemistry, the patient's general history, the unimpaired libido, and a number of other generally supporting evidences, it was felt that diagnosis of functional hypoadrenalism was warranted to the point at least of undertaking experimental medication.

We have been fortunate enough to keep this patient under supervision, and have had opportunities for checking certain of the laboratory findings at not infrequent intervals. During the year 1926 a number of such observations were made, but at the end of this time the patient had so far improved from the clinical standpoint that the frequent checks were omitted. Early in 1928 the patient reported and the improvement previously noted was found to have persisted. Certain of the more significant data can be reduced to tabular form and discussed independently.

TABLE XVI-a

RESPIRATORY METABOLISM

Date	B. M. (%)	B. P. (mm.)	T. (deg.)	Wt. (kgm.)	Dev. (%)
2-1-26	—32	114/72	98.0	64.1	—6
13-2-26	— 7	118/60	97.4	63.8	—7
1-7-26	—11	116/64	97.8	63.6	—7
26-10-26	—26	108/66	97.4	64.6	—6
11-12-26	—23	110/64	97.6	64.9	—5
21-3-28	—18	108/70	98.0	70.1	+2

Inspection of the table shows an improvement in the basal rate to a substantially normal level within the course of a few weeks, and this was maintained with but slight variation for another five months. Following this the summer vacation intervened, and in the fall the patient was found to have lost

on the basal rate and to have slipped back nearly to his earlier level. That he had not been assiduous in following his treatment was freely acknowledged. The blood pressures follow the same general trend, the body weights remain fairly constant. Although medication was intermittent following the last test in 1926, the patient had gained in weight and improved somewhat in his basal level when seen in 1928.

The next table

TABLE XVI-b

BLOOD CHEMISTRY

Values in mgm. per 100cc. blood.

Date	N. P. N.	Urea N.	Uric Ac.	Creat.	Residual	Sugar
2-1-26	47	23	4.8	1.5	21.8	85
13-2-26	42	22	4.7	1.5	17.8	91
1-7-26	43	21	3.9	1.5	20.1	99
26-10-26	38	18	4.2	1.5	18.0	95
11-12-26	32	15	4.7	1.6	14.8	86
21-3-28	36	19	4.7	1.6	14.8	86

shows the changes in the blood chemistry, and here the improvement is very striking. The diminution in the residual nitrogen fraction to a sustained normal level is certainly significant. The rise of blood sugar during the early period of active treatment was also interesting. The blood uric acid was favorably affected as well, but at the time of the last examination it had returned to its original level. A few of the urine sugar values are given in the next table.

TABLE XVI-c

URINE DATA

Date	Vol. (cc.)	Sugar (gm.)
2-1-26	1450	30
1-7-26	1660	16.6
26-10-26	2550	74
11-12-26	1430	71.5
21-3-28	1620	70.6

The lowering of the sugar elimination and its return to a much higher level when dietary restrictions were removed, is obvious from the figures given.

During the period of observation in 1926 a cardiogram was secured which showed a normal organ.

Clinically, it is impossible to furnish sufficient supporting evidence for the diagnosis of "hypoadrenalism" in this case. It is even impossible to state what that evidence should be, since there exists no proven symptom pattern of the condition. There is no doubt, however, that the patient has a definite endocrine disturbance, and the more important symptoms coincide more nearly with those of adrenal impairment, as evidenced in early Addison's disease, than with any other condition known to us. The intermittence of the subjective symptoms is not consistent with the dead level of energy deficiency characterizing thyroid and pituitary deficiency. The undiminished libido would be an enormous stumbling block for any one desirous of explaining the picture on the basis of hypogonadism. The lack of neurological findings renders "piqure" diabetes improbable. And finally, the subjective and objective response to treatment is suggestive, though by no means convincing evidence, that the working hypothesis is correct. Similar responses to treatment have recently been reported by Koehler (31), but we do not share his belief that they can be regarded at present, as an adequate therapeutic test. We are reporting these cases of "hypoadrenalism" because it seems desirable to add to the evidence for or against such a condition rather than because we believe its existence proved.

CASE B-182. The patient's chief complaint was of fatigue and indigestion. She dated the latter from an attack of "ptomaine poisoning" which had occurred some 4 years previously, and which was characterized by abdominal pain, nausea, vomiting, and diarrhœa. Six months later the same group of gastrointestinal symptoms reappeared and had continued intermittently up to the time of her admission for the study. She had lost 17 pounds during this interval but had been underweight at the time of its onset. The condition had been accom-

panied by a marked fatigability which ultimately obliged her to discontinue her occupation which was clerical in nature. At about the time that the symptoms began, brownish pigmented areas developed on the face. These have persisted although there has been some variation in their intensity.

Family History was irrelevant.

Past History: The patient reported minor ailments and influenza at the time of the epidemic. Some time after the onset of the present condition a gastrointestinal x-ray study was carried out which yielded only negative results. In spite of this the patient was placed on an ulcer diet for some time without improvement in her symptoms. She complained of an occasional headache, poor appetite, and flatulency. The menstrual history showed a normal onset, some irregularity with increase in the interval, and a very scanty flow over periods of seven days. Beyond an occasional ache in the lower limbs, the remaining history was entirely irrelevant.

Physical Examination: The patient was a poorly developed and distinctly emaciated girl of 22. A slight dulness at the apex of the right lung and increased vocal fremitus on the right side were reported. Pigmented areas were noted. The right knee jerk somewhat below the normal activity; the remaining findings were normal.

Laboratory Summary: The patient was 36 per cent underweight and had lost nearly one-third of her predicted lung volume. The basal rate was significantly below prediction, and the observed value was somewhat above the truth, as the patient's breathing was very irregular and the trend of the curve not exactly determined. A later measurement showed a value of about —23 per cent, and there was some doubt if this also were truly representative. The blood pressure was at a distinctly hypotensive level; the alveolar carbon dioxide below a normal level. The urine volume was ample but the elimination very poor. Albumin was recorded; no casts were observed. The protein intake was definitely below a maintenance level and this would undoubtedly tend to lower the observed basal rate. The blood nitrogen values were relatively high in view of the low level of protein metabolism. The blood sugar was normal; the sugar tolerance somewhat depressed; the blood morphology was substantially normal.

Radiography: A gastro-intestinal study showed ptosis of the stomach, but conditions otherwise normal. The skull was normal. The left lung showed fibrosis apparently due to an old infection, while the right lung was normal.

Neurological findings were normal.

Pelvic findings were normal.

Eye Examination: The patient showed much enlarged blind spots but otherwise normal conditions.

Discussion: Viewed from the endocrine standpoint, the thyroid could be eliminated by both subjective and objective evidences. With a lowered sugar tolerance and basal rate there is a suggestion of pituitary dysfunction which the enlarged blind spots might be adduced to support. The relative degree, however, of abnormality in these two tests did not conform with the usual pituitary formula. The combination is likewise found with the gonad failure, and here the low alveolar carbon dioxide might be regarded as a supporting evidence. That this low level was in part due, however, to an inability of the patient, through asthenia, to perform the test properly, robs the actual level of something of its authority. With the patient's poor nutrition one would infer a tendency not to lower but to raise the sugar tolerance, on the basis of lack of saturation of the tissues in accordance with Folin's theory. We have observed such a change in under-nourished patients without endocrinopathy who promptly came to a normal level after a short period of proper feeding. There seemed to be no evidence of active tuberculosis, although this again was not rigorously excluded. The patient's asthenia was disproportionate in degree to that observed in pituitary or ovarian cases of a like degree of severity, as indicated by the objective measurements. On this basis a diagnosis of hypoadrenalism was offered tentatively and the experimental application of the Muirhead treatment recommended. The patient was referred from another city. We lost contact with the case and are ignorant of the outcome. While there are several evidences here which are more consistent with a functional adrenal deficiency than with that of another endocrinopathy, we regard this case as distinctly doubtful.

CASE B-323. The patient's chief complaint was of continuous backache, nearly constant headache, abdominal pain, and marked asthenia. In 1900, 25 years earlier, the patient received a severe blow on the coccyx, probably fracturing it. From this time she dates her backache. The coccyxgeal condition was not recognized for over a year, and then operation was regarded as unwise. Coincident with this trauma she developed an obstinate constipation. The menstrual function, which had been normal up to that time, became very irregular, with shortened interval, very profuse flow, and marked dysmenorrhea. After a long ineffective course of ovarian medication, surgery was invoked and a double salpingectomy, uterine suspension, and appendectomy were performed. Following this she became markedly asthenic, developed attacks of syncope, and the menstruation became very scanty; there was no improvement in her general condition. Still later a plaster jacket was applied to the spine and the backache was somewhat better during the period of its use. She was next given a vaccine treatment for arthritis, and finally a diagnosis of mucous colitis was offered. The backache has continued and is seriously inhibiting. She required special arrangements of pillows in her bed in order to lie with any degree of comfort. Latterly she has experienced formication in the lower extremities, also cramps, and deep muscle and bone pains. The onset of her headache was coincident with the initial trauma; it grows worse during the day and is increased by menstruation. It presents the anomaly that the headache subsides in some measure as the flow becomes more profuse. The abdominal pain was situated in the left lower quadrant and came on in the late afternoon. It was of short duration and at times so severe as to produce vertigo. The patient's fatigability has been progressive but is less marked in the morning. At times she is forced to lie down, and while she does not sleep and is conscious of people and of sounds, she is unable to rouse herself. A number of years previously she developed the morphine habit from the therapeutic use of the drug, but the condition was speedily corrected.

Family History disclosed no relevant details.

Past History: In addition to the episodes noted above, the patient recorded the usual children's diseases, abscessed ears and tonsillitis. She had had a tonsillectomy and a dilatation and curettage. She believed that the salpingectomy was performed because of a tuberculous condition of the tubes. The remaining history, including that of the menses, was not remarkable.

Physical Examination: The patient was a well developed and nourished woman of 40. The lips were somewhat cyanotic, the teeth widely spaced. The chest was apparently normal. There was a vague tenderness over the entire abdomen not really localized although possibly increased over the right kidney and in the right lower quadrant. There were brownish pigmented areas on the exposed surfaces, marked tenderness over the coccyx and sacro-iliac region, and a small cystic tumor at the level of the 12th dorsal vertebra over the spine which was not tender. Body hair was heavy but of normal distribution.

Laboratory Summary: The patient's vital capacity measurements were normal. The basal rate at a sub-normal level, with low blood pressure, slow pulse, and slightly sub-normal temperature. The CO_2 output was normal. The urine volume was normal; elimination poor; both albumin and casts were reported. Protein intake was somewhat low. The residual fraction of the urine was definitely above the normal. The 'phthalein test gave a borderline value. The blood chemistry was normal. Sugar tolerance was at half the predicted level. There was a distinct secondary anaemia, and the blood was leucoid in type.

Endermal Tests: The patient was not responsive to a large number of proteins.

Radiography: The coccyx showed a left lateral deviation. The skull was normal as were the spine, sacrum and hips. The caecum was irregularly filled, the appearance raising a question of pylorospasm.

Orthopedic Examination: This confirmed the tenderness over the sacro-iliac region and determined a possible moderate relaxation of the joints. The small tumor growth was designated as a lipoma which was of no importance in the patient's case.

Pelvic Examination gave normal findings.

Eye Examination: Findings were normal.

Audiogram: Showed substantially normal hearing.

Neurological Examination: No organic nerve lesion was disclosed.

Discussion: The condition of the coccyx and lower back seemed to account for her backache. The defect in the function of the caecum could possibly have resulted from adhesions arising from her previous operation. It could also be due to a tuberculous condition, and the questionable pylorospasm could also be referable to either of these causes. From the endocrine standpoint, with a lowered basal rate and lowered sugar tolerance, a pituitary dysfunction, ovarian failure, and adrenal failure were all possibilities. The blood pressure was somewhat low for a pituitary failure; likewise, the blood uric acid was normal and there was no eosinophilia. The eye grounds were normal and there were yet other evidences which rendered a pituitary disorder improbable although not excluding it.

A primary ovarian failure can not be so readily excluded. It is true that the menstrual function showed irregularity and profusion, but the analysis of a long series of ovarian cases shows this particular formula to be the least common. The patient exhibited a definite anaemia, and this we have not observed to be the usual finding in ovarian failure although one to be expected when the adrenal is involved. The normal alveolar carbon dioxide, the leucoid blood, and distribution of body hair, are not characteristic of ovarian failure. As direct supporting evidence for the adrenal, the very low level of blood pressure, the marked fatigability, the evidences of renal impairment, may all be enumerated. The exposed surfaces were somewhat pigmented, and enquiry elicited the fact that none of her family showed a similar coloring. The normal blood sugar is by no means characteristic, but the patient was acutely sensitive to pain and nervously unstable, and this level might represent a slight response to the emotional stimulus which could be engendered in even hypofunctional adrenals. The patient had apparently had tuberculosis in the pelvis, and where tubes are thus involved there are usually other tuberculous areas. On the whole, while the case could not be regarded as clear cut, enough evidence presented to warrant a tentative diagnosis of functional hypoadrenalism. The Muirhead treatment was recommended and was followed for a short time after the patient returned home, with distinct evidence of improvement. It was subsequently discontinued and indirectly we have learned that the patient has relapsed into her earlier condition which is continuing adversely.

Here again is a case in which the main evidence to support the diagnosis is the response to treatment. We have already stated that we do not believe the therapeutic test convincing proof, but it seems worth while to record the findings, as only in this way will enough evidence be accumulated to clear up the very indefinite situation as regards "hypoadrenalism."

Clinically, there was certainly a large element of nervous and emotional instability in this patient, and the time honored diagnosis of neurasthenia can be rejected only because it fails to explain the objective findings. We believe that in this and many other instances the neurasthenia is the result, not the cause, of the metabolic disturbances, and that an attempt at their normalization is at least an essential part of the treatment of patients presenting, in addition to evidences of disturbed metabolism, signs of nervous instability. But we wish to make clear our belief that convincing demonstration of metabolic disturbance is an indispensable pre-requisite to such treatment.

CASE B-505. This is an incomplete case but the evidences are highly suggestive. The patient's chief complaints were of fatigue and fainting spells, tinnitus, and nausea. The patient had been married six years previously, having been well up to that time. Her baby was born five years ago. She failed to regain strength after confinement, and she dated her present condition from that event. She reported that she slept well but was always fatigued, the latter condition progressing during the day. The attacks of nausea developed two years previously and without any predisposing factor so far as the patient could tell. There was no vomiting; there was occasional pain under the left rib border, also low in the abdomen. The onset of the fainting spells was coincident with the nausea, and recently the patient had developed severe attacks of vertigo. The tinnitus was a recent manifestation. Two years ago she learned that her blood pressure was very low.

Family History: Two of three siblings died in early infancy.

Past History: The patient had one or two of the minor childhood diseases and scarlet fever. At the age of 5 she fractured her nose, producing a unilateral obstruction. A few weeks earlier there had been a severe blow to the head but

radiograms of the skull showed no structural injury. She reported an occasional sensation of swelling in the upper eyelids, soft teeth, some chest pain, dyspnoea and palpitation. The bowels were regular but she was troubled with flatulency. The menstrual function had been entirely normal up to 2 years ago when for a period of one year she exhibited shortened intervals.

Physical Examination: The patient was a poorly developed and nourished woman of 26, ambulatory but seeming very weak. Obstruction of the right side of the nose and poor teeth were noted. The pulse rate was somewhat rapid. There was some enlargement of the proximal interphalangeal points; the skin was dark without heavy bronzing, and pilosity on the extremities was marked. The eyebrows were bridged, and there was a slight mustache, also some hair on the breasts. The abdominal hair was heavy but of normal distribution.

Laboratory Summary: The patient was a small woman 12 per cent below her predicted weight and definitely below her predicted lung volume. An unsatisfactory basal rate determination showed —11 per cent with very low blood pressure and somewhat rapid pulse. Repetition of this test was impossible as the patient began to menstruate, returned to her home in another state, and was subsequently felt to be too weak to return for a completion of the study. This episode influenced the completeness of the entire investigation. The alveolar CO_2 was normal. The urine volume was scanty, elimination fair only; both albumin and casts were reported. The protein intake was somewhat low, the residual nitrogen fraction high and the 'phthalein test definitely below the normal. The blood chemistry was fairly normal though the nitrogenous constituents showed an upward tendency in relation to protein intake. The blood sugar was below the normal level. The sugar tolerance was incomplete but was certainly 50 per cent below the normal, and from the amount of sugar excreted during the test probably at a still lower level. The blood showed a definite secondary anaemia without evidence of active degeneration; the leucocytic formula was substantially normal.

Nose and Throat Examination: The tonsils were apparently not offending. The nasal septum showed a sharp deflection to the right.

Pelvic Examination: Conditions were normal except for minor residua of child-bearing.

Eye Examination showed slightly enlarged blind spots; otherwise findings were normal.

Discussion: The whole general picture here is compatible with a condition of failure of the adrenals. The possibility of organic involvement was not excluded, but the incomplete character of the test robs a conclusion of any final authority. Muirhead treatment was recommended, but no further observation of the patient has been possible. Clinically the history is very suggestive of Addison's disease, including as it does the acute exacerbations of weakness and nausea found in our patients with proven adrenal disease.

CASE B-567. The patient's chief complaint was of a swelling of the legs and hips, with marked distention of the scrotum. For the past 10 years the patient had had a chronic arthritis with involvement of the right shoulder and the hips. For the past two years there had been extreme pain at night along the course of the sciatic nerve. For a period of a few weeks before admission there had been much swelling of the feet, while the enlargement of the scrotum had appeared two weeks earlier.

Family History: One uncle died of tuberculosis; the history was otherwise not informative.

Past History: The patient had the minor ailments of childhood, a tonsillectomy at the age of six, and removal of cervical glands three years previously. Six months earlier he had developed iritis of the left eye and had been under continuous treatment for this condition. Some four months earlier he developed a diarrhoea and the use of an acidophilus culture intensified his condition. Under other medication there had been some improvement but he was still passing three or four loose movements daily. He gave a history of a blow on the testicle during boyhood that caused a swelling which subsided spontaneously after lasting for several weeks. He experienced some formication on the legs at such times as they were swollen.

Physical Examination: The patient was a poorly developed man of 25, requiring the use of a cane when walking. The skin was covered with acne, there

was slight ptosis of the left upper eyelid, and the iris was cloudy; there was circumcorneal and conjunctival injection, also moderate photophobia with lacrimation. The right eye was normal. He exhibited herpes on the lower lip, the gums were pallid, and the teeth poor. The left chest was somewhat depressed, producing a definite asymmetry, and the left shoulder drooped downward and forward. The pulse rate was somewhat rapid, the blood pressure distinctly low. Beyond shallow respiration, the lungs were apparently normal. The scrotum was large and distended, and contained a large amount of fluid. The arms exhibited limitation of motion at the shoulder and at the right elbow, with some muscular atrophy. The knee joints were swollen and enlarged, tender, and limited in motion. From the knee down the legs were edematous. There was some bronzing of the skin on the lower extremities.

Laboratory Summary: The patient was slightly underweight and not significantly below his predicted lung volume. The basal rate as recorded was 16 per cent below prediction, with a normal pulse and very low blood pressure. Alveolar CO_2 was a low normal. The urine volume was scanty and the elimination poor. The urine contained albumin and sugar, while the sediment exhibited much epithelial debris and many granular and epithelial casts. His protein intake was inadequate; the residual nitrogen fraction was double the upper normal level. The 'phthalein output was low normal. The blood chemistry showed normal values entirely consistent with the level of the patient's protein metabolism. The blood sugar was low normal; the sugar tolerance, definitely depressed. The blood showed a slight secondary anaemia with an upward tendency to the leucocytes and a slight increase in the lymphocytes.

Examination for protozoa: Repeated examination at night failed to disclose the presence of filaria.

Electrocardiogram: The low voltage indicated an adynamic state consistent with adrenal disease.

Cardiac Examination: The heart was found to be normal. A very low blood pressure was recorded.

Orthopedic Examination: The patient presented generalized evidences of chronic arthritis in all stages of development. At the time of this examination the edema had affected the legs and the body as high as the second or third lumbar vertebra.

Eye Examination: The patient's left eye exhibited subacute inflammation, defined as kerato-iritis, with contracted pupil. The right eye was normal except for a slightly enlarged blind spot.

Radioscopy: Several abscessed teeth were demonstrated; both lungs were hazy, the left auricle prominent; the spine showed a general osteoporosis; there was destruction of the cartilage in both sacro-iliac synchondroses; the right shoulder showed atrophic arthritis; both knees a hypertrophic condition, while the left hip showed both atrophic and hypertrophic processes. The gastro-intestinal appearances were normal.

Chest Examination showed conditions to be substantially normal.

Dental Examination: Several cavities and several infected teeth were demonstrated.

Genitourinary Examination disclosed no abnormality except the scrotal edema and that of the legs. The laboratory evidences did not show markedly impaired renal function.

Stool Examination: Ova and parasites were absent.

Discussion: A study of this case was felt to disclose the existence of two conditions which were by no means necessarily related. In the first place the patient had a definite arthritis of nearly ten years' standing, reported an earlier tonsillectomy, and exhibited a number of infected teeth. Second, there was evidence of nephrosis with edema, but without marked evidence of greatly lowered permeability. While asthenia was not stressed in the history, the patient was markedly fatigable and had been so for some time. The general laboratory picture accorded more nearly with that produced by adrenal failure than by any of the other endocrinopathies. A tentative diagnosis was offered of an early functional impairment of the adrenals. It is, however, recognized that the chronic focal infection, the arthritis, and the renal impairment, might account for most, if not all of the findings.

CASE B-940. This case is included because of the condition found at autopsy. The patient's chief complaint was of pain in the left side of the abdomen and the lumbar region. It had begun some three months earlier, had been progressively more severe and continuous, and was apparently unrelated to any event or habit of the patient's life. There had been a progressive loss of weight—some 40 pounds in the past three months—and a severe asthenia had developed.

Family History was entirely irrelevant.

Past History: The patient had had a few minor ailments in childhood, life-long weakness of the eyes following measles in this period, and one attack of influenza many years before. A tumor in the right breast had been successfully treated by electricity twenty years previously. She reported headache with nausea earlier in life; no attacks for many years. She was subject to rhinitis of a severe type. Though the patient was 68 years of age but few of her teeth had been removed. The appetite had been good until the development of the present illness. With its onset, however, she had developed nausea, flatulency, and diarrhoea. There was apparently an impairment in the sense of taste. Oliguria was a feature of the current complaint, previous to which, however, there had been nocturia. The patient matured early and the menstrual history was uneventful, including the menopause in the early fifties. In years past there had been a mild arthritis in the knees.

Physical Examination: The patient was a well developed woman of 68 showing evidences of much loss of weight. The pupillary reactions were very sluggish; the eyes showed incipient cataracts. There was some septum deviation and a moderate amount of crusting. The gums and teeth were in very poor condition. Smooth, firm masses were detectable over each clavicle, and there were several smaller masses in the neck. The heart gave a blowing systolic murmur, the pulse was slightly rapid. A large mass was felt in the left side of the abdomen with possibly other masses in the epigastric and left inguinal regions. There were several tumor masses on the left thigh, the largest of which suggested a lipoma. There were a number of brownish pigmented areas on the upper body and lower extremities. The knee jerks could not be elicited, and there was a positive bilateral ankle clonus. A generalized adenopathy in cervical, axillary, and inguinal regions was recorded. The distribution of the body hair was entirely normal.

Laboratory Summary: The urine volume was very low and the elimination very poor. Albumin and sugar were both present, while the sediment showed many leucocytes, hyaline, and granular casts. The basal rate was +5 per cent with a somewhat low blood pressure and rapid pulse. The temperature was slightly sub-normal; alveolar carbon dioxide, normal. The patient was 2 per cent under her predicted weight but had lost nearly half her predicted lung volume. Protein intake was low, residual nitrogen high, and the 'phthalein output much below the normal. The nitrogenous blood constituents were distinctly above the normal level. The blood sugar was a high normal. The blood showed a moderate degree of secondary anaemia, and a definite leucocytosis with increase in the neutrophilic elements.

Laryngological Examination: The tonsils were enlarged and infected; the teeth in very poor condition.

Cardiogram: There was some evidence of cardiac impairment of a degree not inconsistent with the patient's age.

Radiography: Numerous infected teeth were demonstrated, and several retained roots. The skull was thickened but was otherwise normal. There was a large tumor mass on the left side of the abdomen reaching below the iliac crest; an additional large mass in the pelvis which showed numerous calcium deposits. The gastro-intestinal tract was normal except for redundant colon.

Eye Examination: The left eye showed an old choroiditis with scars producing an irregular partial central scotoma; the right eye was substantially normal.

Neurological Examination: This confirmed the evidences of a spinal cord lesion previously recorded.

Surgical Examination confirmed the presence of a tumor mass in the abdomen and the generalized adenopathy. The large tumor on the left thigh was diagnosed as a lipoma.

TABLE XVII
"PUBERTAS PRAECOX"

Observation	Sex—Female								
Date	4-29-1925	7-28-1925	10-20-1925	1-26-1926	4-27-1926	6-29-1926	10-19-1926	6-25-1927	7-5-1928
Age (yrs.-mos.)	7-9	8-0	8-3	8-6	8-9	8-11	9-3	9-11	10-11
Height (cm.)	115	121	122.5	124	126.5	127.5	129	134.5	141.5
Weight (kgm.)	22.0	23.8	26.1	28.4	31.7	29.6	31.4	36.1	42.7
Weight Deviation (%)	−3	−5	−2	+4	+12	+2	+3	+9	+10
Lung Volume Deviation (%)	−	−51	−48	−38	−30	−34	−27	−28	−14
Basal Rate Deviation (%)	−29	−10	−18	−8	−24	−18	−24	−28	−21
Blood Pressure Sys.	90	92	100	90	84	86	100	92	116
Dias.	52	58	58	55	48	40	55	50	64
Pulse	94	102	100	92	90	84	84	77	86
Temperature	98.8	99.0	98.8	98.8	98.2	98.6	98.2	97.6	98.6
Alveolar CO_2	34	37	38	42	42	39	33	43	42
Urine Volume	480	850	550	620	570	330	740	560	640
Specific Gravity	1.007	1.010	1.018	1.014	1.019	1.016	1.012	1.024	1.018
Albumin	+	0	0	0	++	+	+	+	+
Casts	0	0	+	0	+	0	0	0	0
Sugar	0	0	0	0	0	0	0	0	0
Total Nitrogen	2.31	4.45	4.90	4.92	4.68	3.30	5.02	5.62	5.10
Residual Nitrogen	13.3	10.3	5.6	13.6	6.2	6.3	8.6	12.5	7.1
P. S. P. 2-hour	53	63	60	68	62	63	55	45	60
Galactose Normal	20	20	20	20	20	20	20 ?	30	40
Observed	20	20	10	10	10	10	30	30	40
Deviation	±0	±0	−50	−50	−50	−50	+50 ?	±0	±0
Blood Non-Protein N_2	34	31	33	−	28	33	26	27	32
Uric Acid	3.3	3.1	4.0	−	3.8	4.2	4.6	2.6	3.3
Sugar	112 ?	107	99	−	105	96	91	93	100
Haemoglobin	85	95	80	95	85	100	95	85	80
Erythrocytes	4.84	4.59	4.35	4.71	4.28	4.97	5.30	5.20	4.40
Color Index	0.88	1.03	0.90	1.01	0.99	1.01	0.90	0.82	0.91
Leucocytes	6.3	4.6	7.6	8.0	10.5	7.2	9.1	7.8	7.4
Neutrophiles	65	48	31	40	47	73	60	56	66
Lymphocytes	30	40	60	45	43	21	30	37	29
Eosinophiles	5	6	2	6	3	1	3	1	1
Endothelials	0	6	6	8	7	5	7	6	4
Misc	0	0	1	1	0	0	0	0	0

Orthopedic Examination demonstrated arthritis in the knees and spine, with possibility of malignant neoplasm in the latter.

Discussion: The case was diagnosed as general carcinomatosis, which was naturally inoperable. She was retained in the Hospital and died some four weeks after admission. At autopsy a large hypernephroma of the left kidney was disclosed with numerous metastases to the lung, liver, and the entire abdominal, peribronchial, thoracic, and cervical lymph glands. The right adrenal was normal. The left was so closely associated with the left kidney that microscopically it formed an integral part of the mass. This case is reported as that of a patient with presumptive destruction of one adrenal and exhibiting certain of the evidences which may be associated with adrenal disease. The normal basal rate constitutes a definite exception, while the patient's alveolar carbon dioxide is higher than that of any other case reported in this group. We have demonstrated in other cases of malignant neoplasm that the sugar tolerance is definitely lowered. The patient had malignant involvement of one kidney, while the other gave evidence of definite nephritic changes. From the differential standpoint the normal basal rate, in spite of the patient's grave condition, rapid loss of weight and lowered nutritional level, is significant. It might be inferred that the value obtained was an algebraic summation of the depleting factors already noted and an upward tendency engendered by the adrenal involvement. This is, however, purely speculative, and in the writers' opinion highly improbable.

From the clinical point of view, it is interesting to compare the findings in this patient with those cited above, and the fact that her symptoms are very similar to those of the other individuals in this group is important. Certainly there could have been impairment of adrenal function in this last patient, and if her symptoms are ascribable to that condition it may fairly be argued that the similar symptoms of the rest of the group might likewise be explained. It is, however, not safe to go so far, since this last patient had an abdominal tumor large enough to bring about mechanically her digestive symptoms, while her asthenia, and many of the laboratory findings may be fairly referred to the general carcinomatosis. So far as our series of cases is concerned it must be said that the case for hypoadrenalism is "suspected but not proved."

Group III. Pubertas Praecox

CASE C-16, et seq. The case of this little patient is reported because of its general interest and of a possible adrenal element. In our opinion this latter is far from established, although there are numerous references in the literature to an association of early puberty with certain types of adrenal disease. Many of these, however, lack objective supporting evidence, and this case is reported without prejudice and for consideration.

The child was admitted to the Hospital late in April, 1925, complaining of a gradually developing weakness of the arms and legs. As a matter of fact she was unable voluntarily to raise arm, leg, or even a finger. The condition dated back to May of the previous year when the child came home from school complaining of illness. After her arrival home she had a severe nose-bleed and vomited, but had so far recovered that she was able to return to school the next day although she complained of a severe headache. As the latter persisted she was kept at home and in bed for several days, during which the tongue became very yellow, and the child apparently temporarily lost the use of her legs. She again recovered from this in a few days but shortly afterward was hit in the right leg which caused her to limp for about three months. The right leg became progressively weak during this period and subsequently weakness developed in the left leg, in the hands, and in the arms. A tonsillectomy was followed by temporary improvement but the child then developed pneumonia some three months before admission to our Clinic. During her attack of pneumonia she was seen by a number of physicians whose opinion was divided between a condition of progressive muscular atrophy and of infantile paralysis. At the time of admission here there was complete inability as noted above.

Family History was irrelevant.

Past History: Beyond the facts already noted the patient had had chickenpox and measles but otherwise up to the time of her illness she had been unusually well and strong. The catamenia had not been established.

Physical Examination: The patient was a well-developed and well-nourished child, seven years and nine months of age. She was unusually alert mentally,

and distinctly mature. The physical findings in the main were normal. The child had no prehensile strength in her hands. The arms could not be flexed at the elbows, nor could the legs and thighs. There was neither adduction, abduction, or flexion in legs and hips; the right leg was somewhat atrophied, and there was foot drop in both extremities. The knee jerks and wrist jerks could not be elicited; there was no ankle clonus. The Babinski and Oppenheim reactions produced flexion. There was abundant hair growth on the legs, arms and external genitalia. The skin was white and free from pigmented areas.

Laboratory Summary: The child was within 3 per cent of her predicted weight. The lung volume could not be ascertained. The basal rate deviation was 29 per cent below prediction. Too much weight should not be given to the absolute magnitude of this datum as standards for female children of this age are far from well established. The relative value, however, is significant when compared with the later measurements. The pulse was distinctly rapid, the blood pressure somewhat low. The urine volume was somewhat scanty, the elimination poor, and albumin was present. The total nitrogen showed an entirely inadequate level of protein metabolism. The residual nitrogen fraction showed an upward tendency. It is to be borne in mind that with lowered protein intake in the normal individual, the relative value of this fraction tends to increase. On the other hand, the patient was a seven-year-old child weighing but 22 kilograms, hence her protein level was not as low relatively as would be connoted by the same nitrogen elimination in an adult. The 'phthalein output was low normal. The sugar tolerance was normal. The blood nitrogen values were relatively high but within the conventional normal limits. The blood sugar was slightly high but this could have been due to an emotional response. The blood morphology showed somewhat low values throughout, the sole exception being a 5 per cent eosinophilia.

Radiography: The spine, pelvis and sella were normal; the skull somewhat rachitic in shape. The mediastinal shadow was 5.5 cm. in diameter. The heart and lungs were normal.

Neurological Examination: A fine muscular palsy affecting the lower extremities, pelvic girdle, and the shoulder girdle was observed. In the examiner's opinion the atrophy was absent which would be expected in a case of anterior-poliomyelitis. Final opinion was reserved.

Discussion: While the child had not established the catamenia, she had a marked growth of pubic hair and the body configuration suggested a beginning maturity. While, as noted above, too great weight could not be placed on the absolute value of the basal rate, it was evident that there was a marked lowering from the level to be predicted in health. The child was under proteinized, which could be a factor, but was not undernourished. There was evidence of a lowered kidney permeability. The child was definitely asthenic; on the other hand the sugar tolerance was normal. It was felt that the illness which the child had experienced had not been properly evaluated. It was impossible to get additional details but there seemed to be no question that the present condition had followed the somewhat vague attack described above. Many of the features were consistent with adrenal impairment, although a thyroid failure could not be excluded with certainty in view of the low basal rate and the normal sugar tolerance. The complementary features of a thyroid failure were, however, entirely lacking. On this basis a tentative diagnosis of adrenal dysfunction was offered and treatment by adrenal cortex suggested. Through the cooperation of the parents, the child was returned to the hospital some three months after our first contact. In the meantime she had been receiving adrenal cortex. It was found that there was a definite improvement in many ways. The whole general musculature had become much stronger, the child was able to raise hands, arms and legs when in a recumbent position. Some atrophy in the extensors of the hands with slight contractions on flexion; foot drop, and marked weakness in the extension of the toes were still apparent. A thorough neurological examination and review of the case, for which we are indebted to Dr. N. H. Garrick, ruled out anterior poliomyelitis and progressive muscular atrophy. In his opinion the vague illness which was the starting point of the whole condition could possibly have been an unrecognized diphtheria, and the muscular condition which was its sequel, a postdiphtheretic paralysis. From the laboratory standpoint the basal rate was found to have increased to the low normal borderline. The patient had grown 6 cm. and increased in weight 1.8 kgm. The pulse was slightly higher, the blood pressure practically unchanged; the alveolar carbon dioxide had increased to a low normal level; the urine vol-

ume had improved, as had the elimination; the protein intake was double, which naturally could have some influence on the improvement in the basal rate. The residual nitrogen fraction was lower, though still high, and the 'phthalein output had increased to a satisfactory normal level. The sugar tolerance remained unchanged. The blood chemistry had improved somewhat in spite of the increased protein intake. The blood morphology showed a slightly lower red count, a slight leukopenia, an increase in the lymphocytes, and a persistence of the eosinophilia. Adrenal cortex medication was continued, and three months later the child was tested again. The weight had improved, the basal rate had subsided to a point midway between the earlier records, sugar had appeared in the urine, the residual nitrogen had become normal, the sugar tolerance had dropped to a level below the normal, a slight secondary anaemia had developed, the lymphocytes had risen to 60 per cent of the normal leucocyte content, while the eosinophilia had disappeared. It is unnecessary to review all of the data of the repeated tests performed on this child in the table given above. Suffice to say that she has regained full use of her arms and hands, there is still a residual toe drop which is being gradually overcome under orthopedic correction. She can walk and run with considerable freedom. The sugar tolerance, while remaining at a depressed level for a period, in September, 1926, exhibited a marked increase to a point above the normal, which was interpreted as indicating an approaching onset of menstruation; this latter was established a few months later, when the child's tolerance became normal and has remained so up to the present time. Adrenal cortex was discontinued after the first marked improvement, and the child has progressed satisfactorily without recent therapeutic aid. The basal rate has remained low, the blood pressure has steadily improved to a present normal level, and the somewhat rapid pulse has given evidences of subsidence. The alveolar carbon dioxide has become entirely normal. The general normalizing of the other factors is apparent from the table. In view of the child's marked improvement it has been felt best to avoid further endocrine medication. She reports yearly to the hospital and a thorough study is carried out. In time it seems probable that it may be wise to resume endocrine therapy. The need for it at the present time, however, has certainly not been demonstrated.

As was stated in the beginning, we have no desire to be dogmatic about this case. It may be permitted, however, to indulge in some speculation, recognizing that it is no more than this. If we assume the accuracy of Dr. Garrick's diagnosis of an earlier diphtheria producing a post-diphtheretic paralysis, we have a patent explanation both for the initial muscular weakness, and equally for its gradual improvement with the passage of time. This, however, would fail to explain the child's early evidences of maturity, and might not entirely account for the very rapid improvement of the muscular condition during the initial phase of her therapy. If the adrenal be a detoxicating organ—and there are many who believe it so to be—it is conceivable that it had passed through a phase of over-stimulation as an incident to the toxaemia arising from the patient's diphtheria. Evidence would seem to indicate that with certain of the endocrine glands such a period of overactivity is followed by a compensatory lowering of functional level. That precocious puberty arises in an overactivity of the gland, is in no small measure assumptive. The presence of a tumor of the cortex does not necessarily connote a functional overactivity, but may imply the reverse. Be that as it may, it is possible that the early maturity of this little patient had its origin in impulses from changed adrenal function which in turn derived from the earlier toxaemia. It is interesting to note that the child's persistent thymus exercised no deterring effect on the progress of her maturation. The case is offered merely for consideration. Continuance of the study may, at some future date, throw light on the underlying etiology. That a thyroid element, as suggested by the present basal rate and sugar tolerance, could enter in, is entirely contrary to the very large number of existing records where thyroid failure at this age has produced a completely opposite effect. That vague and dubious entity, a hyperovarianism, can not be invoked, as at no time had the child shown an increased galactose tolerance with the exception of one observation shortly before the onset of menstruation, and here the fault unquestionably lies with the definition of the standard, and the patient's tolerance was consistent with the physiological stadium. A pituitary factor could find some support, as the child has shown irregularly an eosinophilia, a high blood uric acid, lowered basal rate, and a lowered sugar tolerance. In a long series of pituitary cases, however, we have never studied a patient who showed so marked a depression of the basal rate while exhibiting a normal sugar tolerance. Pituitary cases, transitional between an initial hyper-

and terminal hypo-activity of the posterior lobe, may be studied fortuitously while the sugar tolerance is passing through the normal zone. We have observed a few such cases, checking the accuracy of the initial inference by subsequent study of the case after the transition has been completed. While the anterior lobe seemingly undergoes involutional activity to a hypofunctional level more readily and rapidly than the posterior lobe, we have never observed a case in which the anterior lobe has been so far ahead of the posterior in its transitional adjustments. Finally, a stimulating influence on the genital sphere is observed in overactivity, not failure, of the pituitary. The case for the pituitary then would seem to lack substantial support, and we feel constrained to conclude that if the patient be endocrinopathic the adrenal would seem to be the most probable focus of involvement.

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THE RELATIONSHIP OF IODINE TO THYROID HYPERPLASIA AND FUNCTION*

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The literature upon thyroid disease is so voluminous, the ideas expressed are so varied and many of the papers are so abstract that physicians who have not made a special study of goiter are more confused after reviewing the literature than before beginning such a study. It is time for those who are making an actual study of the thyroid and its pathology to sift carefully the wheat from the chaff and state in a definite, clear and concise manner the present status of our knowledge.

The clinician's interest in goiter centers around three major problems. First, the insuring of a normal thyroid gland at birth; second, the prevention of goiter; and third, the treatment of goiter in those patients in whom it has been permitted to develop.

Halstead in 1896 stated that congenital goiter could be produced by the removal of a greater portion of the thyroid gland of a pregnant female dog, but that the removal of a major portion of the thyroid gland of the male had no influence upon the thyroid of the progeny. Experimental work has confirmed Halstead's observation. A study of the patients with congenital goiter whom I have seen in private practice and in the goiter clinic of the University of Oregon has led me to the conclusion that congenital goiter in the human is of exactly the same origin. That is, if the mother's thyroid gland is not secreting enough thyroxin during pregnancy, a demand is thrown upon the child's thyroid gland to function in utero. As the result of this demand, there is either a secretion of colloid resulting in a colloid goiter, or a hyperplasia resulting in one of the types of hyperplastic goiter. Congenital goiter thus produced is not then an hereditary disease, but is instead a congenital condition developing as a compensatory process. So true is this that whenever we see a family in which all or nearly all of the children have goiter, we can with practically a hundred per cent of accuracy predict that the mother had a goiter, and although the thyroid gland may have been able to produce sufficient secretion under ordinary conditions, it was deficient when the added load of pregnancy was thrown upon it. I have yet to see the first patient with congenital goiter borne by a woman with hyperthyroidism, and I do not believe it occurs. By that, I do not mean to say that a woman who has a deficient thyroid during pregnancy may not as a result of the stimula-

*Read at the Twelfth Annual Meeting of the Association for the Study of Internal Secretions, Minneapolis, June 12, 1928.

tion thrown upon that gland, develop a toxic goiter subsequent to the pregnancy.

The problem then in preventing congenital goiter is assuring a sufficient amount of thyroxin to care for the needs of both mother and child. In women with normal thyroid glands, this can be done by maintaining an iodine intake sufficient to enable the thyroid gland to produce the necessary thyroxin. If the iodine in the food and water is deficient, more must be added. To the woman with a thyroid so deficient that it cannot produce the necessary amount of thyroxin, dessicated thyroid is given. Iodine should not be given to the woman with a non-toxic goiter of the adenomatous type, as it is liable to be made toxic thereby. Some time ago I conceived the idea of giving the patients of this group a small amount of dessicated thyroid. This has been done by my associate in the goiter clinic, Dr. C. E. Brous, and although his experience at the present time is too limited for a positive statement, we believe that this is going to be the solution of the prevention of congenital goiters in children of women with glands of the type which make it unsafe to give iodine.

The causes of goiter may be classified as primary and secondary. The primary causes of goiter are first, and chief, a deficiency in the iodine intake; second, anything that lowers the ability of the thyroid to utilize iodine; and third, anything that increases the thyroxin need above that which a partially deficient thyroid can produce. Iodine deficiency as a cause of goiter is an undisputable fact and is universally accepted by everyone who has made a really scientific study of the problem. The relationship of the existence of goiter and iodine deficiency in the great goiter belts, such as the Great Lakes Basin and on the Pacific Coast where the surface water, and hence, the vegetation, is deficient in iodine, cannot be doubted. The best proof of this statement occurs in northern Michigan, where there is one district in which practically everyone has an enlarged thyroid and in which the surface water is absolutely devoid of iodine.

The iodine intake in food and water may be sufficient, deficient, or relatively deficient. It is sufficient when there is a sufficient amount of iodine to meet the demand for thyroxin at any time and in any amount. It is deficient when there is not enough iodine to meet the need even under minimum activities. It is relatively deficient when there is a sufficient amount of iodine to produce the necessary amount of thyroxin under ordinary conditions but not enough to produce the necessary amount of thyroxin when there is an extra load demanding an increased amount of thyroxin. Examples of this are seen in individuals who, under ordinary conditions, have normal functioning thyroid glands, but who develop a goiter as a result of excessive physical or mental strain or disease.

The thyroid in its ability to utilize the iodine furnished to it must be classified as efficient, deficient, or relatively deficient. The efficient thyroid gland is able to utilize iodine and produce the necessary amount of

thyroxin under all conditions. The relatively deficient gland is the gland that under ordinary conditions is able to produce a sufficient amount of thyroxin, but when the demand comes for more thyroxin, it is not able to produce it even though there is a sufficient amount of iodine. The deficient thyroid gland is the gland that is not able to produce thyroxin enough under any circumstances even though there is plenty of iodine at all times. Both the deficient and the relatively deficient glands may be unstable either because of a congenital abnormality or acquired changes.

Glands that are relatively or absolutely deficient, or in which there is a relative or absolute deficiency in the amount of iodine intake because of the regenerative power of the gland, may develop any of the hyperplastic forms of goiter. If the congenital goiter in man, as that in experimental animals, is the result of a maternal thyroxin deficiency, we can trace back most of those goiters which have not been the result of an actual disease of the gland to a primary iodine deficiency in the maternal ancestor, and while there are other determining factors that have an influence in the development of goiter, they are, in reality, playing secondary rôles. The perfectly normal thyroid gland, which is receiving a sufficient amount of iodine, will not develop a goiter, but a perfectly normal thyroid gland receiving an insufficient amount of iodine or a thyroid gland with lowered efficiency produced by infection or toxins or other lesions so that it cannot utilize the iodine that it receives, usually results in the production of some form of goiter.

The prevention of goiter in the individual born with a normal thyroid gland is merely that of supplying a sufficient amount of iodine. We hear a great deal said about the danger of iodized salt, but the experience of using the iodides in syphilis in the days gone by has demonstrated conclusively that it does not carry any danger to the ordinary individual. The danger is only to the individual with the abnormal thyroid gland and it is my personal opinion that it occurs only in the thyroid which has undergone a hyperplasia so that there is a markedly increased number of cells which have been lying dormant and may be stimulated into activity by the giving of iodine over a long period of time.

A comparative study of the acini of the colloid goiter with that of the normal thyroid gland indicates the type of treatment required. The cells secrete two known substances; one, thyroxin, and the other, colloid. Colloid appears to be an inert substance filling the acini, its purpose being either that of holding the iodine in suspension until needed for the production of thyroxin or holding thyroxin in suspension until needed. I am personally inclined to believe that it is the former. When in the presence of an iodine deficiency, a demand is thrown upon the thyroid gland for more thyroxin, the cells set about trying to produce it. In this attempt, there is an over-secretion of colloid distending the acini. As the acini become distended with colloid, the margin is stretched, flattening the cells both by the stretching their bases and the increased intra-acinar pressure due to increase in colloid. In well marked cases, the cells become so flat-

tened that the protoplasm at the sides of the nuclei is not as thick as the nuclei. Such cells can not be expected to secrete normally.

A few years ago in the goiter clinic of the University of Oregon Medical School, we divided our patients with simple colloid goiter into four groups. One group was given ten milligrams of iodine daily, one group was given one grain of sodium iodide three times daily, another group was given larger amounts, and another group was given one grain of dessicated thyroid daily. The patients were seen every two weeks and the thyroid gland examined, the neck measured, the pulse counted, and other observations made as indicated. The length of the treatment varied from a few weeks to two years.

Later three of us independently went over the records and came to the same conclusion, viz.: iodine does not cure simple colloid goiter in a majority of cases, but dessicated thyroid does. In the iodine series, the results were practically the same regardless of the amount. A few were cured. The most of them were not. Some of the goiters on iodine decreased in size and then increased while iodine was being given. Experimentally, we have shown that the increase in colloid begins within two days after reducing the thyroid capacity by operation and that if there is not some relief, the hyperplasia begins within a week. That hyperplasia does not take place in all glands is, I believe, due to the fact that the added stimulation enables the thyroid to utilize the iodine to a better advantage. There is no organ in the body that is one hundred per cent efficient, and we have no right to believe that the thyroid gland is absolutely efficient. With an increased activity on the part of the cells, it may utilize the iodine to a greater degree of efficiency than it was doing before. This I think explains the reason for not getting the early hyperplasia in all colloid goiters.

The fact that the giving of iodine to patients with colloid goiter does not produce results in a majority of such patients is due to this deficiency of the cells. The treatment then is to put these cells at rest by supplying the thyroxin already prepared until the colloid can be absorbed and the cells come back to normal. It has been our custom in the goiter clinic of the University of Oregon to give patients with a simple colloid goiter one grain of dessicated thyroid three times a day. Occasionally some patients require more. It has been our general experience that patients with a simple colloid goiter are cured within a period of two or three months. So firmly are we convinced of the truth of this statement that to those patients in whom cure does not result in that period of time, we state that there has been error in the diagnosis. We have seen the patient too late when hyperplasia had already occurred. This we have proved by operating upon some of them who later became toxic and finding a diffuse adenomatous type of goiter.

In the treatment of toxic goiter, iodine in the form of Lugol's solution has been found invaluable in the preparation of the patient for operation, regardless of the type of goiter. It must be used, however,

with caution. It must not be used indiscriminately, as some patients are harmed by the prolonged use of Lugol's solution. It has been our experience that when this has occurred, these patients do not readily yield to Lugol's solution again.

So far I have dealt with the use of iodine in the preparation of the patient for operation. In reviewing the literature, we find frequent references to patients who have not been cured. Some time ago I made a study of the patients seen in the goiter clinic who have been operated upon without a complete cure. As a result of this, we were able to classify the patients of this group as follows: First, errors in diagnosis, that is, the symptoms the patient had were not due to a thyroid lesion; second, late operation, the patient having had permanent lesions produced previous to the operation. The operation had cured the goiter and there was no longer any hyperthyroidism, but the patient still had a damaged heart and nervous system and symptoms of goiter present because of these permanent lesions; third, incomplete operation, in which case the patients have never been cured; fourth, true recurrences.

To study the cause of true recurrences, we carried on experimental work on dogs and rabbits and found, first, that it was possible to remove a minimum amount of thyroid without producing any reaction in the thyroid gland at all. In other words, we left enough thyroid gland to produce the necessary amount of secretion so that there was no need for any compensatory change. Second, we found that when the maximum amount of the thyroid gland was removed, leaving only a very small portion, there were certain uniform changes that always occurred. These were first, an increase in the amount of colloid which appeared within two days, and second, a hyperplasia that began at the end of the week. Third, we found that when an amount between these extremes was removed, if the animals were given iodine there would be no reaction; but, if they were not given iodine, hyperplasia occurred. Our experimental animals could be classified in their relationship to thyroxin production as follows: first, thyroxin efficient, in which there was enough thyroxin produced to meet the animal's need; second, relatively deficient, in which, when iodine was not given, the hyperplasia took place because there was a thyroxin deficiency, but when iodine was given, hyperplasia did not take place because the cells were able, with an excess of iodine, to produce enough thyroxin; and third, thyroxin deficient, in which there was not enough thyroid tissue to produce the necessary amount of thyroxin even though the gland was kept saturated with iodine. In this group, hyperplasia always took place.

We next studied the influence of iodine upon the hyperplasia. There had appeared in the literature a discussion between Loeb and Marine as to the effect of iodine upon hyperplasia. We found that when the gland was kept saturated with iodine by giving Lugol's solution, the hyperplasia continued usually up to about the end of the third week, occasionally a few days longer, there being two exceptions in which it was not completed

within a month. We found, further, that when iodine was not given, the hyperplasia was much more extensive and in two instances it produced an actual goiter in dogs that had a normal thyroid gland before operation. In no instance did we see a goiter develop in a dog that received a sufficient amount of iodine during the period of regeneration.

We then applied this to our patients. The patients all have the thyroid gland saturated with iodine previous to the operation by giving Lugol's solution in 10 to 25 minim doses, three to four times daily, according to the severity of the goiter. Following the operation, we give Lugol's solution in 15 to 30 minim doses by rectum the first two days, three or four times a day. After this, we give 10 minims by mouth three times daily for the first month following the operation, and then 10 minims once a day for the next month, and then follow up with iodized salt or iodine tablets. Since we have followed this regime, we have seen just one patient who has returned with a toxic goiter, due to excessive regeneration. This occurred in a foreigner who could not understand English well and had neglected to take the Lugol's solution as directed.

SUMMARY.

We may sum up our present knowledge of the relationship of iodine to the thyroid gland as follows:

1. Iodine constitutes a high percentage of the thyroxin molecule and is therefore essential to its secretion.

2. Goiter develops as the result of the continued iodine deficiency in the diet.

3. Congenital goiter occurs in the presence of a thyroxin deficiency in the mother and can be prevented by maintaining a sufficient iodine intake for the mother with a normal thyroid gland and giving dessicated thyroid to the mother with a deficient thyroid.

4. Goiter can be prevented in those born with a normal thyroid gland by maintaining sufficient iodine intake unless the efficiency of the thyroid is later lowered by disease.

5. Iodine relieves hyperthyroidism but does not cure in the majority of cases and should be used only for preparing patients for operation.

6. The thyroid gland should be kept saturated with iodine following subtotal thyroidectomy in order to prevent excessive regeneration.

7. Following regeneration a sufficient iodine intake must be maintained in order to prevent recurrence.

A STUDY OF THE STIMULATING EFFECT OF THE TESTICULAR SUBSTANCE ON SUGAR METABOLISM

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There are reported in the literature contradictory results on the effect of castration on metabolism. Loewy and Richter (1), for example, found that the removal of the ovaries decreased oxygen consumption and that the administration of dried ovaries to these castrates increased it, while Lüthje (2) on the contrary found that castration in dogs of both sexes had no influence on metabolism. Mitchell finds that castration of cockerels lowers their basal metabolism (3).

It is recognized that castration produces a profound change in the activity of an animal. A very active, unruly and pugnacious animal, such as a bull or stallion for example, becomes very subdued and easily managed after castration. Hoskins (4) found that castration greatly decreased voluntary activity and that testicle grafts failed to bring about any significant improvement in activity. Increased activity is always accompanied by an increase in metabolism, and since the animal derives most of its energy from the metabolism or oxidation of sugar, it was thought desirable to study the effect of the testicular substance on sugar metabolism.

The respiratory quotient is the index usually used to the amount of sugar metabolized, a rise in the quotient indicating an increase in sugar metabolism, and a fall a decrease. In this investigation, sugar utilization, as well as the effect of the testicular substance on its utilization, was determined directly according to the following procedure.

Seven hundred cc. of 0.1 per cent dextrose solution was prepared and divided into portions of 100 cc. These 100 cc. portions were introduced into beakers. Twenty mgm. of the testicular substance* were introduced into one beaker, and 40, 60, 80 and 100 mgm. into other beakers. Two gold fish of approximately the same size and with a combined weight of approximately 5 gm. were then introduced into the beakers. Air was bubbled through the sugar solutions to insure an adequate supply of oxygen to the fish. The two beakers containing gold fish and sugar solutions to which nothing was added served for controls. Sugar determinations were made according to the method of Benedict immediately and after 30 hours. The averages for 4 series of experiments are shown in Figure 1 under "testicular substance." It will be seen that the average amount of sugar used in 30 hours by the controls was 22 per cent and that the fish in the

*The testicular substance used in this investigation was a Parke, Davis & Co. preparation. It is sold under the name of "Orchic Substance" and one grain of the powder represents 10 grains of the fresh gland.

sugar solutions to which 20, 40, 60, 80 and 100 mgm. of testicular substance were added used 54, 67, 74, 77 and 78 per cent of the sugar respectively. By comparing these figures it will be seen that the testicular substance increased sugar utilization and the greater amount of the substance used, the greater the increase produced.

One of us had already shown that the ovarian substance increased sugar utilization in the unicellular animal, Paramecium. The object of repeating this work and reporting it in this paper was to determine, in the first place, if the ovarian substance would increase sugar utilization in a higher animal, such as the gold fish, just as it was found to do in

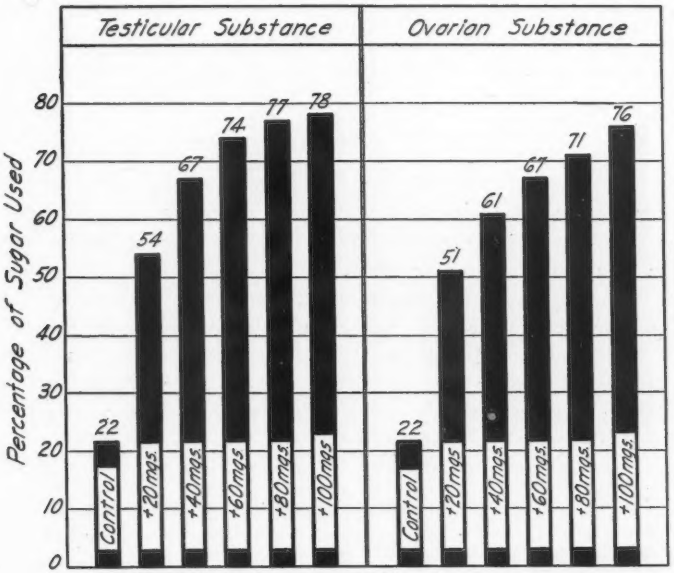

Fig. 1. Chart showing the stimulating effect of varying amounts of the testicular and ovarian substances on sugar metabolism.

the unicellular animal, and in the second place, to compare the effect of the ovarian substance with that of the testicular substance, using the same kind of animal.

The method of procedure with the experiments with the ovarian substance* was identical with that used with the testicular substance. As a matter of fact the experiments were made at the same time and under identical conditions, and for that reason, as may be seen in Figure 1, the controls used exactly that same amount of sugar, for the controls were the same in both series of experiments.

It will be seen in Figure 1, under "ovarian substance," that the fish to which 20 mgm. of ovarian substance were added used 51 per cent of

*The ovarian substance used in this investigation was a Parke, Davis & Co. preparation. It is sold under the name of "Ovarian Substance" and one grain of the powder represents six grains of the fresh gland.

the sugar against a control of 22 per cent, and the fish to which 40, 60, 80 and 100 mgm, were added used 61, 67, 71 and 76 per cent of the sugar respectively. By comparing these figures, it may be seen that the ovarian substance increased sugar utilization just as did the testicular substance.

The following precautions were taken and checks made in the preceding experiments. Air was bubbled through sugar solutions for 30 hours without the presence of fish and it was found that this had practically no effect on the sugar solution. Air was also bubbled for 30 hours through sugar solutions into which had been introduced the testicular and ovarian substances without any effect on the amounts of sugar in the solutions. It was found that the sugar was used only when the fish were present and the utilization ceased upon the removal of the fish. From these observations it was concluded that the fish were responsible for the utilization of the sugar observed in these experiments and not bacteria or yeast.

SUMMARY

1. The effect of various amounts of testicular substance on the rate of sugar metabolism of gold fish was studied. It was found that this substance stimulated sugar metabolism, the greater the amount used, the greater being the stimulating effect.

2. Ovarian substance also stimulated sugar metabolism of the gold fish, as it had been found to do in the unicellular organism, Paramecium.

3. It is concluded that both the testicular and ovarian substances would be found to have the same effect on the higher animals and man if the effect in these instances could be tested out directly as was done in the experiments reported in this paper.

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THE STRUCTURAL CHANGES WHICH TAKE PLACE IN THE THYROID GLANDS OF GUINEA PIGS DURING THE PROCESS OF COMPENSATORY HYPERTROPHY UNDER THE INFLUENCE OF IODINE ADMINISTRATION

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In two previous publications (1) we have studied the effect of iodine administration on compensatory hypertrophy of the thyroid gland in guinea pigs; in a more recent, not yet published, series, we have extended these observations. In this paper we wish to correlate the facts thus established concerning the effect of iodine on the growth processes taking place in the thyroid gland with structural changes associated with these growth processes. In addition we shall refer more briefly to more recent experimental studies of Gray and Loeb (2) and of Rabinovitch (3) from our laboratory in which a marked effect of the administration of potassium iodide on the mitotic proliferation in the normal thyroid gland of the guinea pig was established. Furthermore, we wish to point out some of the problems still to be solved and to suggest some way in which previous observations concerning the effect of iodine on the thyroid gland might perhaps be harmonized with results obtained by Gray and Loeb, and by Rabinovitch.

We shall compare the conditions found in animals to which KI has not been administered (controls) with those observed in guinea pigs which have been under the influence of KI (iodized animals).

1. *A comparison of the growth processes* in general in these two groups of animals shows that administration of KI does not prevent compensatory hypertrophy, but on the contrary makes it, on the whole, more pronounced. The number of animals showing hypertrophy was greater in the iodized animals and, furthermore, the average intensity of this process was also greater in the latter. However, in making these comparisons we must take into consideration the fact that, as a result of the stimulation caused by KI in the thyroids of these guinea pigs, secondary changes take place in the course of time which tend to obscure the hypertrophy. In the iodized guinea pigs definite changes occur in the character of the colloid, which cause an increase in the contents of the acini and thus lead secondarily to an increase in the pressure exerted on the whole wall and above all on the epithelial lining of the acini. Furthermore, the growth of the thyroid during compensatory hypertrophy does not take place through apposition of new acini in the periphery of the gland, but it con-

sists in an increase in the number and size mainly of the epithelial cells of the acini, although an occasional mitosis may also be seen in the stroma, in particular in the vascular endothelium. Thus, as a result of the growth itself, the pressure within the gland remnant must be increased and must lead to conditions which are injurious, if the surrounding tissue opposes the necessary expansion of the gland. However, at no time do we see degenerative changes taking place in the thyroid gland which could be interpreted as caused by the iodine administration as such. Where no pressure is exerted on the gland cells they appear normal; in general neither cytoplasmic nor nuclear degenerations are noticeable. But even where pressure may secondarily obscure the hypertrophy of the gland, we can always find indications that these secondary changes affected cells which had previously been hypertrophic; however, very often we observe in the iodized guinea pigs a marked increase in the size and mitotic proliferation of the acinus cells and also an increased prominence of granules, in that part of the hypertrophic cell which adjoins the colloid. Occasionally we see, in such acini, multiple elevations consisting of hypertrophied epithelium protruding into the colloid. It is probable that these blunt papillae are due to growth processes taking place under conditions which do not permit a free expansion, although we must consider also the possibility that similar prominences may develop as a result of perforations in the wall separating adjoining acini. In rare cases, the epithelium, instead of protruding into the lumen of the acini in the form of papillae, may push, in an outward direction, into the underlying stroma.

2. *Modifications in the character of the colloid during the process of compensatory hypertrophy in controls and in iodized guinea pigs.* The characteristic change which takes place in the colloid during compensatory hypertrophy consists in softening and in solution processes. While it occurs in both controls and iodized animals, it is much more pronounced in the latter. Inasmuch as during the liquefaction the colloid takes up water and thus acquires a greater volume, certain consequences may result. It is possible that not only liquefaction but also an increased new formation of very soft colloid takes place. In some acini very soon the more or less liquefied colloid, which stains only very slightly or not at all with eosin, in contrast with the hard colloid of resting glands, which stains intensely with eosin, is absorbed, whereas in others it is retained, thus exerting pressure on the walls, especially on the epithelial lining of the latter, and causing a distension of the acini. In other instances, in which the absorption has progressed very far, the cavity of the acini becomes transformed into slits, lined by hypertrophic, high epithelial cells, in which the granular character of the cytoplasm is very distinct. Where the liquefied colloid has largely been retained, a gradual flattening of the epithelium, as well as a thinning of the walls, takes place as a result of the pressure. We can now find all transitions from the original hypertrophic epithelium to the epithelium flattened by pressure; if the latter

changes have become very pronounced, it may be difficult to recognize that this condition developed from a preceding state of hypertrophy.

If only a softening of the colloid has taken place without an actual liquefaction, we find this substance still taking the eosin stain, but less intensely than in the normal, less active gland. Because of its softness, the colloid is sticky and it adheres to the epithelial lining of the acini with threads, between which are found vacuoles of different sizes. This peripheral layer of vacuoles is quite characteristic of this type of colloid. Whether the formation of these vacuoles is due to solution processes in the peripheral colloid, which take place under the influence of the adjoining epithelial cells, or whether they are due to a retraction of the colloid caused by dehydration, which occurs during the process of fixation and embedding of the tissue, or whether it is due to both these processes combined, cannot be decided definitely at the present time. This condition is related to that observed in the normal gland, where in general the hard colloid is slightly retracted from the epithelial lining, evidently as the result of the shrinking taking place during the embedding of the tissue; but owing to the hardness of the colloid, the retraction in this case is very slight, whereas in the more watery colloid, which develops during compensatory hypertrophy, the retraction is much greater. Between these various states we find all degrees of transition and we can also observe different stages in the process of softening and solution of the colloid. Thus we not rarely find in the cavity of an acinus a more solid plate of colloid in the center, surrounded by a peripheral pale zone, in which the solution of the colloid has advanced much farther. We would interpret this condition as indicating that the liquefaction process proceeds in the direction from the outside towards the center. In other cases the outlines of the colloid have a ragged appearance, as though eaten out by some dissolving agent; or in still other cases we may see a pale plate of colloid, surrounded by an entirely liquefied zone. Occasionally we note in a disc of pale, soft colloid a number of red round spots, which represent either particles of colloid, that have resisted the solution processes longer than others, or which represent the remnants of phagocytes, which have undergone degenerative processes and which thus have become converted into balls not unlike colloid. It seems that phagocytes in the colloid may undergo such a type of degeneration. All these changes we may observe, although with unequal frequency, in the controls as well as in the iodized animals.

There is reason for assuming that these softening and solution processes are caused by a substance, presumably of an enzymatic character, which is given off by the epithelial cells when they are in a state of stimulation, such as we find during the process of hypertrophy, and perhaps the prominence of granules in that portion of the cells directed towards the lumen of the acinus indicates the preparation of enzymatic substances on the part of the epithelium. These solution processes, although occur-

ring also in the controls, are proceeding on the whole with much greater intensity in the iodized animals.

However, there exists a second mode by which the colloid can be dissolved, namely, through the action of phagocytes; the latter succeed in dissolving the colloid locally, either directly, or they may first take little particles of colloid into their cell body and thus destroy it; which of these two processes prevails is difficult to decide. Subsequently these phagocytes degenerate, either by karyorrhexis or by karyolysis, and thus leave cavities in the colloid at the point where they have been. The cavities developing in this manner are usually of the size of the average phagocytes, but occasionally they may be larger, probably owing to a swelling which these cells undergo during the process of degeneration. Thus isolated or multiple holes may develop in the colloid and often a honeycombed appearance may be produced; in extreme cases only a few shreds of colloid may remain. However, these phagocytic cells succeed in causing such a localized solution of the colloid only in case the latter substance has already previously been softened to a considerable extent; they are unable to dissolve the hard colloid usually found in the normal non-stimulated gland, especially in the peripherally situated acini. Also this phagocytic activity is much more pronounced in the iodized animals during the process of compensatory hypertrophy than in the controls; and the same difference between the phagocytic activity in these two classes of guinea pigs we find also in the intact thyroids of animals which have not previously been submitted to a partial extirpation of this gland, as Gray and Loeb, as well as Rabinovitch, have shown.

There is still a third way in which a solution of the colloid can take place, namely, through the activity of the polymorphonuclear leucocytes. We have observed this condition in only one case in a control animal, in which evidently some infection had taken place, although the guinea pig had gained in weight during the course of the experiment. In this case the whole gland presented a honeycombed appearance; thin and compressed walls separated large, irregularly shaped acini, filled with very pale and partly dissolved colloid or with colloid which had still a slightly greater consistency and which therefore took on a light pinkish color and was much retracted, changes which indicated that certain solution processes had taken place. In some of the large acini these solution processes in the colloid had gone so far that frequently only shreds of colloid were left. While the epithelial cells were often somewhat vacuolar, they were still enlarged, owing to compensatory hypertrophy which had taken place, and they showed frequent mitoses, notwithstanding the pressure exerted upon the walls of the acini. As the result of this pressure, the latter were in various places in process of perforation and in the end only remnants of them in the form of spurs were visible. In the lumen, as well as in the walls of many acini and in the tissue surrounding the gland, there were numerous polymorphonuclear leucocytes, which were largely responsible for the marked solution processes occurring in the colloid, the intensity

of solution in a definite location corresponding to the number of leucocytes present. Also in the vessels of the tissue surrounding the thyroid remnant there were many leucocytes, whereas in the perivascular areas we observed masses of lymphocytes together with an admixture of polymorphonuclear leucocytes. In addition some mononuclear phagocytes were found in the remaining parts of the colloid.

We may mention here that there exists still another condition in which solution of the colloid takes place, namely, in autolysis; for instance, in thyroid tissue kept in vitro under unfavorable circumstances we observe a marked liquefaction of this substance.

We see then that in principle the same solution processes occur in the thyroids of iodized as well as in the control guinea pigs, but they are more pronounced in the former; also the absorption of the liquefied or partly liquefied colloid is here less rapid, and thus in the iodized guinea pigs this material collects to a larger extent in the acini and distends them. However, there is only a quantitative difference existing between these two sets of guinea pigs, as in both an accumulation as well as an absorption of the liquefied colloid occurs, but in different degrees.

Furthermore, we see not only differences in different individuals in the degree of hypertrophy of the cells and in the intensity of solution processes in the colloid of the gland remnants, but even in different parts of the same gland. Thus in both controls and iodized guinea pigs there is, on the whole, a greater tendency on the part of the colloid to remain solid in the most peripheral acini. This is associated with a lowered activity of the epithelium, which is flatter here, whereas in the center the collod is on the average softer and the hypertrophy of the epithelium is more pronounced. There is perhaps also, in the iodized animals, a greater tendency towards the absorption of the softened and liquefied colloid in the central acini and to its retention in the peripheral acini. We suggest that these differences between the central and peripheral acini are not, as has been maintained, due to differences in the embryonal origin of these gland constituents, but to differences in the vascularization and perhaps also to differences in pressure effects, which exist between the peripheral and central areas of the thyroid. The central portions of the gland seem to be under more favorable conditions in this respect than the peripheral parts. However, hypertrophic processes occur also in the peripheral acini and may be especially prominent in the iodized guinea pigs.

In describing the conditions observed in the colloid we may briefly refer to two minor changes which may here occur. Not rarely we observe the remnants of hemorrhages in some of the acini; in such cases the extravasated blood may either form a dense disc or ball in the center of the colloid or in some cases it may lie crescent-like on the periphery of this substance. It is probable that these hemorrhages are due to trauma inflicted upon the thyroid at the time of the operation, when parts of the gland tissue were extirpated. Furthermore, trauma, in particular pressure exerted on certain peripheral parts of the gland remnants, may cause a

pushing of cell masses into the colloid, which thus in some areas may almost entirely fill the cavities of such acini.

3. *Pressure effects in the gland remnants of the control and of the iodized guinea pigs.* As we have mentioned, there are two factors which may lead to pressure effects in the thyroid gland, namely, (1) growth processes of a non-appositional character, taking place in the gland and associated with the usual production of colloid; (2) changes taking place in the colloid and consisting in the production of a large amount of solid material, which, instead of being absorbed, remains in the lumen of acini. This condition is found especially in the peripheral acini in normal glands, where the colloid is hard and present in a relatively large quantity; but even in hypertrophic gland remnants there is still a tendency for the colloid in the peripheral acini to be harder than in the central areas. There is a third factor which may lead to pressure, namely, a very rapid and intensive liquefaction of the colloid due to the taking up of water, which causes an increase in volume of the contents of the acini, a liquefaction which may or may not be associated with an increased production of colloid. We find this condition in certain acini in compensatory hypertrophy of thyroid remnants, but it becomes much more prominent if animals during the process of compensatory hypertrophy are fed or injected with KI. Also in otherwise normal guinea pigs, in which the thyroid gland has been left intact, Gray and Loeb, as well as Rabinovitch, observed in the later periods of KI administration a tendency on the part of the colloid to liquefy. In the iodized animals with compensatory hypertrophy,—and a similar condition we find in animals in which the thyroid has been left intact in the late stages of iodine administration,—the liquefied colloid has in general less tendency to be absorbed than in controls, which are in the process of compensatory hypertrophy, and thus this substance, accumulating in the gland, necessarily exerts pressure on the walls separating adjoining acini. This pressure will make itself felt more in the center of the wall than near the corner points where neighboring acini adjoin each other. It leads first to a flattening out of the epithelium which affects more or less the whole lining of the acinus; but it acts also on the stroma and in particular on the capillaries in the wall, which latter, on the one hand, supply the tissues with necessary substances, and, on the other hand, serve as an instrument through which absorption of the contents of the acini takes place. Both these processes must therefore be interfered with, if the pressure becomes strong enough. The pressure on the epithelium also has certain consequences. The mitotic proliferation in the epithelium decreases and, when the flattening out of the epithelial layer has become very pronounced, it ceases altogether. Furthermore, we may assume that the pressure and consecutive flattening of the wall will also interfere with the production and secretion of colloid and presumably also, in the end, with the production and secretion of the enzymes which, as we may suppose, are responsible for the diffuse solution which takes place in the colloid in cases of compensatory hypertrophy and which is

so much increased in iodized guinea pigs. At last the wall separating two adjoining acini may become in places a thin flat band and it may break through in the center. It is only in exceptional instances that we see the epithelium, at a point where the pressure is greatest, become necrotic preceding the perforation; no sign of degeneration outside the pressure effects is noticed in the thyroid acini under usual conditions. As a result of these perforations adjoining acini are thus united. At first, spurs, representing the remnants of the wall, still project into the lumen and indicate the place where the perforation has taken place. Then the contents of the acini unite and the spurs may become gradually shorter and in the end may disappear; thus two or even a larger number of medium-sized acini may have joined in the formation of one very large acinus, in which all indications of such an origin have disappeared. It appears probable that when such changes have taken place in acini in which the colloid has become liquid, the latter may be gradually absorbed, if the epithelium, now forming the walls of the larger, new acinus, functions again and then a secondary decrease in size in such acini may take place owing to the pressure exerted by the surrounding tissue. Thus we may explain an apparent incongruity in certain cases between the relatively small increase in size of the whole thyroid or of the thyroid remnant and the considerable mitotic cell proliferation which has taken place under these conditions. Similar perforations are found in peripheral acini of normal glands when, as we have seen, the large amount of solid colloid exerts a certain pressure, and thus even here a constant transformation in structure occurs, but perforations seem to be much more frequent, as far as we can judge without having actually made comparative counts, in glands which are in the process of compensatory hypertrophy and especially in animals receiving at the same time iodine. During compensatory hypertrophy they are seen not only in the peripheral parts of the gland, but also in the central areas; and in such structures we have to deal not only with narrow thin spurs projecting into the lumen of the acini but also with papillae lined with hypertrophic cells. The latter kind of projections may owe their origin to perforations which took place in walls in which the epithelium either had already undergone compensatory hypertrophy at the time of perforation or which underwent hypertrophy subsequent to the time of perforation. We find all transitions from this condition to that in which the wall of an acinus is lined by hypertrophic epithelium, projecting into the lumen of the latter in the form of multiple short and blunt papillae. The origin of such multiple projections is not certain. They may be due to growth processes during which the proliferating epithelium is forced to fold and to protrude into the lumen of the acinus, or they may represent the remnants of multiple perforations, in which a number of adjoining acini are at last united into a single acinus.

There still remains to be explained the fact that, in so many acini in which liquefaction of the colloid takes place in iodized guinea pigs during the process of compensatory hypertrophy, the more or less fluid

material is not absorbed, but remains in this condition and causes distension. However, as we have seen, this is not always the case in iodized guinea pigs; even in these a considerable absorption of this fluid may take place similar to that usually seen in controls during the process of compensatory hypertrophy; conversely also in the latter a retention of fluid may occur. But a quantitative difference exists in this respect between these two classes of animals, and two factors are perhaps responsible for the lack of absorption in the iodized guinea pigs. In the first place there may be so great a rapidity in the solution process in the colloid that it leads to early pressure effects, which interfere with the absorption of fluid. Associated with this process there may perhaps be also a more active new formation of fluid colloid. In the second place, there may be, as a result of the stimulation by iodine, so much hormone carried into the circulation that a saturation occurs and thus mechanisms are set in motion which inhibit this excess elimination of colloid into the circulation. However, it is not probable that after extirpation of so large a part of the gland the organism as a whole is supplied with such an excess of hormone. Furthermore, the localized appearance of this retention in the gland renders it more probable that we have to deal with local factors like pressure rather than with general effects or the whole organism and with regulations following these effects. Moreover, in the peripheral acini of normal glands, the retention of colloid and consecutive pressure effects, which, we observe, must be explained as due to localized conditions. On the other hand, the retention of softened or liquefied colloid in the whole glands of iodized guinea pigs, which is found especially in later stages of iodine administration, is probably due to an over-activity of the gland, taking place under the stimulus of iodine, not accompanied by a sufficient discharge of this material and therefore followed by pressure effects. We must consider the possibility that a regulatory mechanism diminishing the absorption of colloid may play a part in the latter kind of cases.

4. *On the character of the phagocytes found in the colloid of control and iodized guinea pigs.* In discussing the solution processes in the colloid, we have referred already to the activity of phagocytes, which cause a localized softening and solution of the colloid and which later degenerate. These phagocytes appear in especially large numbers in the iodized animals, although they may be numerous also in the controls. They are found preferably in acini in which the colloid is softened and has therefore become somewhat paler. They are not usually found in acini in which the colloid is completely liquefied or has become absorbed. In case the colloid is still hard, there are either no phagocytes present or they are small or merely the nuclei remain visible. This condition is observed in control as well as in iodized animals; also in the former the phagocytes are more numerous and larger, in places where the colloid is pale and soft. The phagocytes in the controls are therefore on the whole more frequent in gland remnants, which show a higher degree of hypertrophy, probably because the softening of the colloid follows a course parallel with the

degree of hypertrophy. However, it is possible that in addition to the action of a mechanical factor certain metabolic processes in the acinus epithelium, or in the colloid adjoining the epithelium, may attract the phagocytes.

In hard colloid the phagocytes cannot produce solution processes, but here they seem gradually to degenerate and disappear; perhaps also the separation of solid balls out of the colloid may be due to the activity of these cells. In soft colloid phagocytes take up particles of this material and dissolve it; they may then swell and after degeneration leave holes in the colloid which are very large.

The phagocytes may take up also isolated red corpuscles which have entered the colloid, or occasionally they may enclose even desquamated epithelial cells. In rare cases mitoses or the presence of two nuclei can be observed in such phagocytes.

While, as stated above, degeneration usually leads to solution of the phagocytes, following karyorrhexis or karyolysis, it seems that some of these cells may become transformed into round bodies, staining intensely with eosin and thus, in the end, resembling solid colloid material, which is perhaps identical with the solid balls in the colloid to which we have just referred. In addition we occasionally observe, in the colloid, cells with dense eosinophilic cytoplasm and a central round intensely staining nucleus; these cells are similar to those which may occasionally be seen in the epithelial lining of the acinus. They also represent, probably, an early stage of degeneration.

As to the origin of the phagocytic cells, certain observations which we made may be of interest. In certain cases, in iodized as well as in control animals, we noticed connective tissue breaking through the wall of the acinus into the colloid. Here some cells, situated in the connective tissue, rounded off, detached themselves from the rest and became phagocytes. It seems, then, that certain stroma cells may undergo this transformation. On the other hand, we also observed that, as a result of growth processes in the epithelial lining of the acini, the epithelial cells were pushed in the direction towards the cavity of the acinus; they then desquamated, finding there less favorable conditions in the supply of oxygen and food stuffs. In view of the fact that epithelial cells lining the acinus may take up particles of red corpuscles or of pigment derived from the latter, it is not improbable that also the desquamated epithelial cells may act as phagocytes. In addition we must consider the possibility that lymphocytes, which seem to be increased in the stroma of iodized guinea pigs, may migrate into the colloid, increase here in size and thus become converted into phagocytes.

5. *Structural variegation as a characteristic of the thyroid remnants in iodized animals.* We have seen that certain structural characteristics are usually associated in the acini of the thyroid gland. Thus, almost complete liquefaction of the colloid is, as a rule, associated with distension

and enlargement of the acinus, while at the same time a gradual flattening of the hypertrophied epithelium through pressure occurs and ultimately perforation and spur formation. The colloid does not take the eosin stain well and appears, therefore, pale. Medium-sized acini may be associated with pinkish colloid, containing a peripheral zone of vacuoles, and with a markedly hypertrophic epithelium. Fargoing absorption of the softened colloid is, in certain cases, observed in acini in which the lumen has been reduced to the form of irregular slits; in these the epithelium shows marked hypertrophy and the cytoplasm of the latter is distinctly granular. Solid, slightly retracted colloid is found in medium-sized or small acini with low or medium-sized, not hypertrophic, epithelium. However, in the peripheral zone of the thyroid, the acini, in which we find this type of colloid and epithelium, may be large, as a result of a preceding pressure perforation and union of neighboring acini. In addition, between these types of acini various transitions may be observed; furthermore, in the same gland remnant the appearance may be somewhat different in different parts. However, whereas in the control animals this latter condition is not very prominent, it is characteristic of the gland remnants of iodized guinea pigs. Here we often find, within the same gland remnant, areas with large acini and almost liquefied colloid, alternating with somewhat smaller acini, with partly absorbed and faintly pink staining colloid, or with pink staining, vacuolar colloid; in some cases we may observe in the center the appearance of slits. It is this variegated appearance in the iodized animals, and especially the presence of foci containing large acini with pale, largely dissolved colloid, which is characteristic of the gland remnants of the iodized guinea pigs. In the control animals the structure is usually much more homogeneous, the large majority of the acini, in many cases, showing somewhat hypertrophic epithelium and slightly softened pink-staining colloid in medium-sized or slightly enlarged acini. However, in both iodized and control animals areas may appear in which the colloid is hard and hypertrophy of the epithelium is lacking; but, as stated by us previously, in our experience such areas are more common and on the average more extensive in control animals. Thus this variegated appearance makes it possible in many, although not in all cases, to distinguish the thyroid remnants of iodized from those of control animals. It follows from what we stated above that the differences between these two classes of animals are not absolute, but only relative and of a quantitative character.

DISCUSSION AND CONCLUSIONS

We may consider it as proven that in the guinea pig potassium iodide, either given by mouth or injected interperitoneally, does not prevent compensatory hypertrophy. On the contrary, the number of cases in which compensatory hypertrophy is lacking is, in our experience, on the whole greater in the controls than in the iodized animals. This conclusion holds good irrespective of the size of the thyroid gland tissue which we leave

behind at the time of operation, within the limits tested by us. It holds good if we leave as much as one half of one lobe; also within the ranges of daily doses of 0.01 and 0.05 grams KI. Even with a daily dose of 0.1 gm. which would correspond approximately to so large an amount as 12-15 grams of KI in an adult man, the hypertrophy was not necessarily prevented, although it was, on the whole, diminished. As to the cause of the diminished hypertrophy in this latter case several factors have to be considered. In the first place the guinea pigs receiving so large a dose of iodine showed a relative loss of weight or at least a considerably smaller gain than the animals receiving a smaller dose. Now, we have observed previously that gain in weight during the course of the experiment favors the development of compensatory hypertrophy, whereas its absence, or even a loss in weight diminishes considerably the chances of compensatory hypertrophy. The unfavorable weight balance of the group receiving 0.1 gram KI daily, which was noticeable in our cases, may, therefore, at least partly explain the relative diminution in hypertrophy observed. The actual or relative loss in weight in this group may be accidental or it may be due to otherwise injurious effects of so large a dose of iodine; it is, however, also possible that, at an early period in the administration of such an amount of this substance, a pronounced functional stimulation of the gland takes place, leading to the production of an excess of thyroxin, which counteracts the stimulating effect of the iodine, and which thus would tend to induce a return of the thyroid to a resting state. While we cannot exclude this possibility,—and at later stages even in animals receiving the smaller doses of KI—still we can be certain that it is above all the pressure exerted on the walls of the acini by the increase in their content, in particular by the swelling and liquefaction of the colloid, which causes the flattening out of the epithelium and ultimately the perforation of the walls separating adjoining acini.

It is also this same factor which plays a part in reducing, in the course of time, the extraordinary increase in proliferative activity which takes place in the normal thyroid gland of guinea pigs, under the influence of administration of KI (Gray and Loeb, Rabinovitch); but in this case we have again to consider at least the possibility that ultimately an excess of thyroxin is produced, as a result of the increase in iodine intake, and that thus a tendency to the reduction in thyroid activity may follow at a later stage.

As to the marked increase in the content of the acini, it is essentially due to the taking up of water by the colloid and its subsequent softening and liquefaction. This process occurs in the controls as well as in the iodized animals, but with a much greater intensity in the latter, and thus there may result, in this group of animals, an early development of pressure, acting on the walls of certain acini, and an interference with the rapid absorption of the fluid which has accumulated in the acini. However, as we stated above, there exists in this respect only a quantitative difference between the controls and the iodized guinea pigs; in both groups

absorption as well as retention occurs, and in iodized as well as in normal glands the retention is, on the whole, more marked in the peripheral acini, where apparently the circulatory conditions are less favorable.

Another factor which may also play a rôle in diminishing absorption is perhaps an excess of thyroxin in the organism. Such an excess might result from its increased production following the administration of iodine. Our experiments, showing that compensatory hypertrophy is prevented by administration of thyroxin to a guinea pig, prove that it is the amount of active hormone present in the whole organism which here determines the productivity of the gland. In addition there may be a mechanism which regulates the rapidity with which thyroxin is given off by the thyroid gland and which may act in accordance with the needs of the whole organism. Uhlenhuth, especially, has emphasized the necessity of postulating a mechanism regulating the discharge of colloid as distinct from that regulating its production (4). It is not very probable, however, that an excess of thyroxin, as a limiting cause for the discharge of the colloid from the acini, would come into play after extirpation of the greater part of the thyroid gland, which in itself reduces the amount of hormone produced, but it might conceivably do so in normal guinea pigs which receive iodine, particularly at a time when softening of the colloid becomes noticeable. Furthermore, it is possible that this increase of content in the acini in both classes of iodized guinea pigs, those in process of compensatory hypertrophy as well as those in which the gland has remained intact, is not only due to an increased retention of colloid, but also to an increased production of colloid, which takes place under the influence of iodine administration.

The liquefaction of the colloid, which is thus so markedly intensified through the administration of iodine, is characteristic of a stimulated condition of the thyroid gland in general, except when special factors like infection or autolysis play a part. This softening and liquefaction is presumably due to an agent given off by the epithelial cells of the thyroid; it therefore presupposes an increased epithelial activity and the latter would be called forth by a stimulus developing as the result of the lack of thyroxin in the organism. Corresponding to this stimulated functional condition are the structural changes which we have described, namely, an increase in size of the epithelium and an increase in number and size of the cell granules in compensatory hypertrophy, with and without feeding of iodine. As we have seen, the latter substance increases the number of cases in which compensatory hypertrophy occurs, until such a time as secondary effects, in particular the pressure exerted by the excess of material in the acinus, produce injuries in the epithelium. The increase in the number of phagocytes in the thyroid of iodized guinea pigs is also indicative of a condition of stimulation.

There is an apparent discrepancy between the effects of iodine administration in the guinea pig—as observed by ourselves in compensatory hypertrophy and by Gray and Loeb as well as by Rabinovitch under normal

conditions—and in the dog, where Des Lignéris (5) and subsequently Marine (6) observed a filling of the acini with solid colloid. In human beings also, to judge from recent investigations concerning the effect of iodine in cases of Graves' disease, a solidification of the colloid may follow the administration of this substance. Perhaps the difference is more apparent than real. We may consider the possibility that in both cases iodine stimulates the thyroid gland; but whereas in the dog, and, under certain conditions also in man, such a stimulation leads to an over-production of colloid, which may exert pressure on the acinus wall and thus secondarily and at least temporarily reduce the activity of the gland; in the guinea pig this stimulation apparently leads to the increased preparation of a substance, perhaps of an enzymatic nature, which tends to liquefy the colloid.

As to the comparative number of mitoses in cases of compensatory hypertrophy in normal and in iodized guinea pigs, we have not yet made exact counts and can not, therefore, make definite statements; we know, however, that compensatory hypertrophy as such produces increased proliferative activity in the thyroid gland. Furthermore, if we compare sets of gland remnants in control and in iodized animals, the number of mitoses seems on the whole to be greater in the latter, because here the hypertrophy is more marked, if we compare all the experiments in both sets of guinea pigs. On the other hand, we have also observed that the increased pressure exerted by the liquefying colloid on the wall of the acini and the subsequent flattening of the epithelium tends to diminish the number of mitoses; when the pressure effects are not yet very pronounced, mitoses may still be found, but with increased pressure and flattening of the epithelium they gradually cease. This factor would thus tend to limit mitotic proliferation, especially in the iodized guinea pigs; it will, however, be necessary to make exact counts before definite data in this respect can be given.

As to the cause of the increased number of mitoses in compensatory hypertrophy, it is due to the stimulation which the lack of a sufficient amount of thyroxin in the organism sets into motion. The extraordinary increase in mitoses, which occurs in normal glands under the influence of iodine administration, is presumably due also to the direct stimulation which iodine exerts on the thyroid epithelium; but there may come into play, in addition, the effect of a slight increase in the content of the acini, which tends to stretch the acinus cells and to separate them from each other, and which thus may alter the action of contact substances by means of which neighboring epithelial cells influence each other and which normally restrict proliferative processes. Possibly also the mechanical stretching, as such, may set into motion proliferative changes. Thus a great increase in proliferative activity would be produced. How far the direct stimulation of the epithelial cells by iodine and how far a secondary process of stimulation, which primarily has called forth a slight softening of the colloid, come into play in this process, cannot be determined with certainty at the present time.

It is also of interest that iodine in compensatory hypertrophy has the opposite effect on colloid as well as on hypertrophy of the gland, which we noted in the case of administration of thyroid (Armour and Co.)(7) and of anterior pituitary substance (Armour and Co.)(8) in this condition. Both of these substances, if fed by mouth, tend to inhibit compensatory hypertrophy in the guinea pig, and to prevent the softening of the colloid, which, on the contrary, is found to be hard. The constituent of the anterior pituitary which exerts this effect is unknown at the present time; but it is probable that it is a substance which differs from those hormones of the anterior lobe of the hypophysis which stimulate the growth of the organism as a whole and which stimulate the development of the ovaries.

SUMMARY

Administration of potassium iodide in the guinea pig, during the process of compensatory hypertrophy of the thyroid gland as well as in the normal guinea pig, causes a stimulation of the gland tissue, in which softening and solution processes as well as increased growth processes are noticeable. In the case of the normal gland the growth processes which are initiated by iodine are very prominent, whereas in the case of compensatory hypertrophy, where the removal of a great part of the gland tissue as such causes a marked stimulation, the changes in the colloid are more pronounced. It is shown that the structural changes thus produced in compensatory hypertrophy make it possible for us in many cases to recognize whether iodine has been administered during the process of compensatory hypertrophy. The various changes induced by the administration of this substance have been discussed and also the possible relationship which these changes have to each other.

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THE INFLUENCE OF ANTERIOR PITUITARY EXTRACT ON THE SEX GLANDS AND GROWTH

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Until recently there have been many divergent views regarding the functions of the anterior pituitary gland. The results reported by Evans (1923-24) and his co-workers led us to try some similar experiments. The following brief history of the relationship between the sex glands and growth and the anterior lobe of the pituitary gland illustrate the divergent views of the various investigators.

Schafer (1912) reported that feeding of pituitary tissue to rats had little or no effect on growth or metabolism. Wulzen (1914) claimed that fresh anterior pituitary gland, when fed to chicks, caused a retardation of growth and involution of the thymus. Goetsch (1916) stated that the feeding of the anterior lobe of the pituitary gland caused more rapid growth and earlier sexual maturity in both male and female rats. This investigator also reported that the ovary of the pituitary-fed rats had large numbers of corpora lutea. Marinus (1919) reported somewhat similar results. After feeding desiccated anterior lobe to the domestic fowl, Pearl (1916) found that there was no earlier activation of the ovary nor was there any increased egg production.

Tethelin prepared from the anterior lobes by Robertson (1916) was claimed to increase the growth of mice. These results were not confirmed by Drummond and Cannan (1921). Sisson and Broyles (1921) reported that there were no changes in the normal development of rats after feeding desiccated pituitary gland. C. S. Smith (1923) obtained negative results upon feeding the anterior lobe. These experiments were carefully controlled so that the results appear to be conclusive. That ovulation in the fowl was inhibited by intraperitoneal injections of fresh anterior lobe was reported by Walker (1925). That this result was not an effect due to intraperitoneal injections of either muscle extract or of Locke's solution was demonstrated. Feeding of fresh anterior pituitary glands to hypophysectomized rats did not prevent the changes resulting from this operation (P. E. Smith, 1927).

Crafts and Flower (1924-25) found males to remain fertile which had undergone for some months the same daily dosage of anterior hypophyseal fluid which in their sisters has led to cessation of ovulation. Evans

and Simpson (1926) found gigantism to be produced in males as well as females by such injections. By the end of the fifth month there was demonstrable a clear diminution in sex response as determined by refusal of the male to copulate with different females in active oestrus. With one exception, however, copulation was always eventually accomplished and production of healthy litters resulted. Autopsy of two cases showed great relative and considerable absolute diminution in testes weights with smaller tubules but with no evidence of degenerative changes—facts in agreement with the persistence of normal morphology of spermatazoa in the fresh ejaculate.

Evans and Long (1921) studied the effects of injections of anterior lobe hypophyseal extract on the oestrus cycle in the rat and found an immediate cessation in the four-day rhythm, smaller doses permitting oestrus to recur at longer intervals, larger doses inhibiting it altogether. On section of ovaries the characteristic picture was that of ovulation having been prevented apparently through some toxic influence exercised on the ova, but instead of follicular healing through death of granulosa and hypertrophy of the thecal cells the granulosa also had taken on growth changes and corpora lutea were produced enclosing the imprisoned ovum. In these rats either the rate of formation of corpora or their survival exceeds that typical for normal ovaries for approximately twice as much lutean substance exists in these ovaries as in normal controls. These investigators found that in addition to germ cell injury and toxicity to developing embryos there was a specific stimulant to lutean cell growth in these cases.

Since these experiments were started P. E. Smith (1927) has reported a series of investigations on the induction of precocious sexual maturity by pituitary transplants. Similar results have also been reported by Zondek and Aschheim (1927). Recently Putnam and Benedict (1928) described increased growth of skeleton and increase of the size of the nipples in a bulldog produced by intraperitoneal injections of anterior hypophyseal extract.

PROCEDURE

For the pituitary injections fifty-four albino rats about 30 days of age and averaging 40 gm. in weight were divided into four groups of 12 rats each and a fifth group of 6 rats. For the most part correspondingly numbered rats in each group were litter brothers or litter sisters. About half of the animals were male and the rest female. The protein injections were made into a different group of rats which had a separate control group. Five female rats were injected with a liver extract of known protein content.

An attempt was made to feed a diet adequate in every respect. The principal food of the pituitary injected rats and their controls was a mixture of casein 20 parts, butter 20 parts, dried brewers yeast 5 parts, inorganic salt mixture No. 32 3 parts, agar powder 1 part and corn starch

51 parts. This diet was given on the average five days a week. For the other two days a mixed diet of fresh lettuce, beef heart, cheese, bread and ground whole yellow corn was given with a view to supplementing any unknown deficiencies in the standard diet. The rats used for the protein injections and their controls were fed on a diet consisting of whole yellow corn, oats, milk and table scraps.

Three pituitary extracts were prepared and called Nos. 1, 2, and 3 and were injected into the animals of groups I, II, and III respectively. Group IV was a control group given no treatment and Group V was fed an amount of Extract 1 corresponding to that injected into the animals of Group I. Extracts were injected intraperitoneally every other day, one-half cc. portions being given for the first two weeks, then 1 cc. portions for 1 month and finally 2 cc. portions for the remaining injection period.

The extracts were prepared as follows:

Extract I was prepared from the carefully dissected anterior lobes of ox pituitaries.* After grinding in a food chopper they were ground in a ball mill for 4 hours with twice their weight of 0.2 normal acetic acid. The acid was neutralized with sodium hydroxide and the precipitate formed was removed by filtration. This precipitate was dissolved in dilute sodium hydroxide and acid added to the neutral point. After filtration, the filtrates were combined and evaporated to the appropriate volume. Each cc. of the extract represented 1 gm. of the anterior lobes.

Extract II was made by adding an equal volume of saturated ammonium sulphate to Extract I before it was concentrated. After filtering off the precipitate formed it was ground with two separate portions of 50 per cent ethyl alcohol. To this alcoholic extract an equal volume of 95 per cent alcohol was added. The precipitate was placed in solution in water. Each cc. of this extract was equal to 3 gm. of the fresh gland.

In making Extract III eight volumes of 95 per cent alcohol was added to the filtrate from the precipitate used for making Extract II. As before the precipitate formed was dissolved in water. Each cc. represented 3 gm. of the fresh gland.

The liver extract was prepared by the method which Evans (1923-24) used in preparing pituitary extracts. Fresh calf liver was cut into small pieces placed in 40 per cent ethyl alcohol, the alcohol was allowed to drain, washed in sterile saline and then ground for one hour in a sterile ball mill. After adding a half volume each of sterile saturated sodium bicarbonate solution and of sterile saline, the paste was stirred. This paste was neutralized, using litmus as the indicator. After centrifuging this material, the supernatant liquid was placed in tubes. Each cc. of this extract represented about 1 gram of the fresh liver tissue. The total protein nitrogen varied from 444 to 649 mgm. per 100 cc. of extract. Before these extracts were placed in sterile test tubes, 0.1 per cent tricresol was

*These glands were obtained as fresh as possible from the stockyards and kept on ice, but it was 24 hours or more after they were removed from the animal before they were extracted.

added as a preservative. They were kept in a refrigerator until used. All of these extracts gave the ordinary protein color tests. The injections were made intraperitoneally, using sterile syringes and needles.

Females injected with pituitary extract were observed for the development of pregnancy. At 110 days, 125 days and 150 days typical males and females from each group were killed, examined for any gross abnormalities, ovaries and testes removed, fixed and sectioned. No gross pathological changes were noted in any of the animals. The record of pregnancies is given in Table I.

TABLE I

INFLUENCE OF PITUITARY EXTRACTS ON DEVELOPMENT OF PREGNANCY

Group	No. of Animals	No. of Females Pregnant After Days					
		80	100	120	150	175	200
I	6	0	0	0	1	0	1
II	6	0	0	3	1	1	
III	6	0	0	2	1	3	
IV	4	4					
V	4	4					

Note.—In Group I one female killed at 110 days was non-pregnant, and two killed at 150 days were non-pregnant, and in Group II one animal died.

For determining the effect of protein injections on the sex organs and oestrus cycle, vaginal smears as well as histological sections of the ovaries were made. The technique used was that of Frank.* A moistened toothpick was inserted into the vaginal canal and withdrawn. The toothpick was then stirred in a small drop of water on a clean slide. After drying in the air and fixing by passing through a flame several times they were stained for thirty seconds with a one per cent aqueous solution of thionin. The diagnosis of the smears was made microscopically and the classification of oestrus cycles made according to the classification of Long and Evans (1922).

The results on growth are shown in Charts I and II. In Chart I the average rates of growth of females are shown and in Chart II the average rates of growth of males. In Chart I the growth curves are terminated with the development of pregnancy. As Group V contained only six rats instead of twelve, the slightly greater growth of animals of this group, which were fed pituitary extract, is not conclusive. Nor can any favorable influence of either of the three extracts studied on growth be said to have been shown by these experiments. Evans (1923-24) in a similar period of treatment obtained differences in weight of nearly 100 grams, or 50 per cent. As Evans found the growth promoting substance to be

*Frank, R. T. Personal communication.

thrown down by 50 per cent alcohol, our negative results with Extracts II and III are not unexpected. Our Extract No. I was made with dilute acetic acid. The one chiefly used by Evans was an extract in normal salt solution from which the author states that most of the protein may be precipitated by making the solution 0.03 N with acetic acid without loss of hormone. One cc. of our extract corresponded to 1 gm. of fresh gland, that of Evans to 2 gm. Our injections were made every other day using about twice the daily amounts used by Evans. Evans started injections at 14

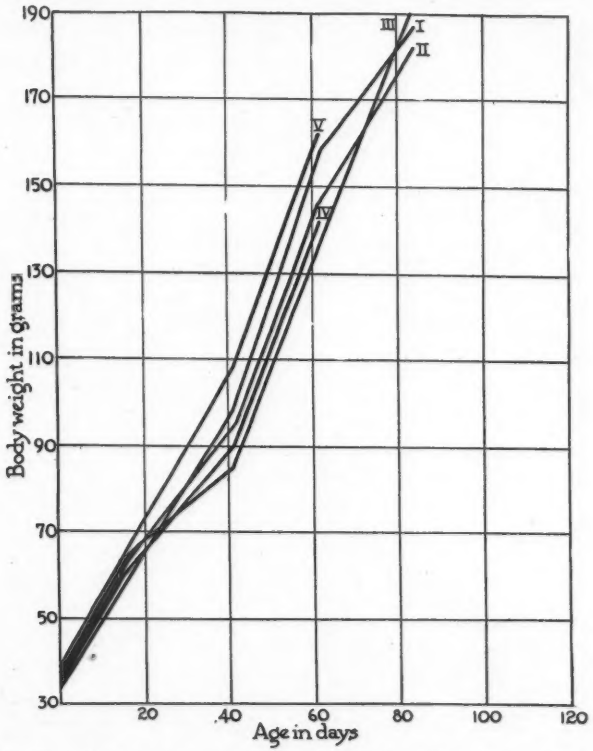

Chart I. Growth of female rats following injections of anterior pituitary extracts. Weights are averages for groups. Group IV is the control group.

days of age and we at 30 days. Our diet was planned to furnish adequate vitamine so that such substance present in the considerable amounts of extract injected could not be expected to be of influence. Evans does not describe the diet of his animals, but the controls grew well. From our results it seems as though there was actual retardation of growth rather than acceleration. Ours were acid extracts, whereas Evans made an alkaline extract which was later acidified. Though our extracts were not prepared from glands which were as fresh as those used by this investigator, the extracts were preserved with 0.1 per cent tricresol and kept cool; there

was no putrefaction at any time. For an explanation of the difference between our results and those of Evans, the most probable cause seems to be that we made an acid instead of an alkaline extract. The extract which was made by precipitating the proteins present by half saturation with ammonium sulphate, then triturating the precipitate in 50 per cent alcohol and reprecipitating a part of the soluble material by adding equal volume of alcohol, was not expected to give any growth effects. This was definitely stated by Evans. The Extract III, though it did produce some

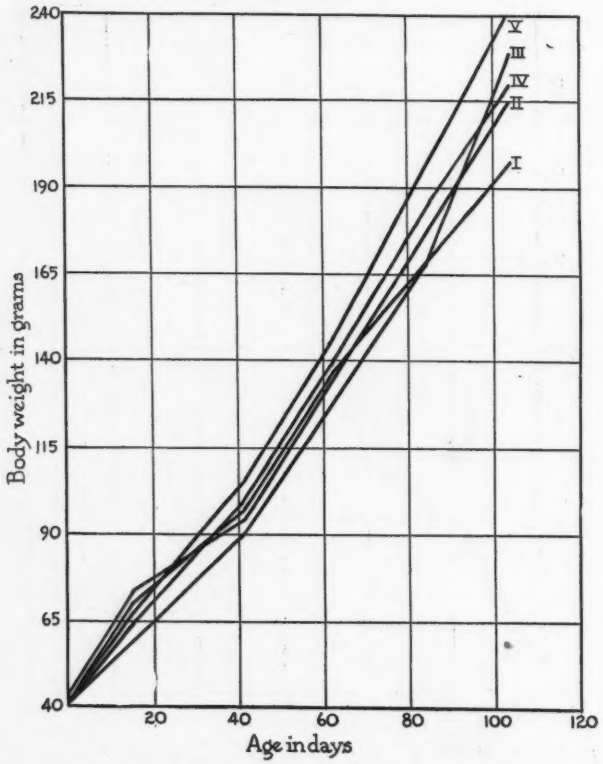

Chart II. Growth of male rats following injections of anterior pituitary extracts. Weights are averages for groups. Group IV is the control group.

retardation of pregnancy, did not, however, show much action on the ovary as judged microscopically. The liver extract was injected because it was thought that this toxic action on the ovary of the pituitary extracts was due to their protein content. The vaginal smears of these five rats showed that the oestrus cycle occurred every fourth or fifth day the same as the control rats. The retardation of the oestrus cycle described by Evans must be a specific action of the anterior pituitary extract produced when it is injected intraperitoneally into rats.

The following is a general summary of the ovarian findings: The sections of the ovaries of the rats in series I were all very similar. There were atypical Graffian follicles in various stages of development. The tunica seems to be normal. The few ova that are present are small. The granulosa has disappeared in most cases, but in some it has proliferated rather extensively. In several cases, the ova seem to be imprisoned by the rapidly proliferating cells which have come from opposite sides of the follicle so that the ova have assumed an elongated form. The cells of the corpora lutea are not of the usual large type but are much smaller and are arranged in cords separated by spaces almost equal to the cords.

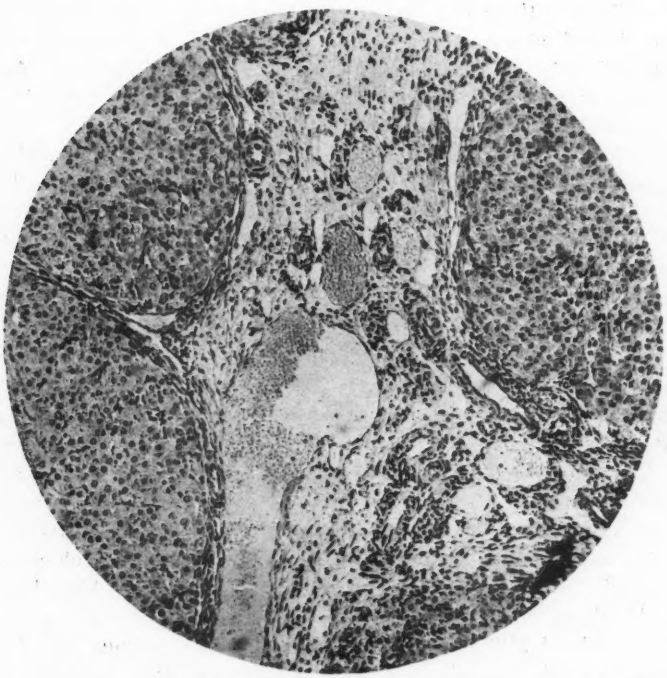

Fig. 1. Microphotograph of a section of the ovary of a rat receiving pituitary extract. Corpora lutea formation has been decidedly stimulated.

In one of the sections in this series, the granulosa has proliferated but, instead of producing lutean cells, has failed to differentiate so that there are structureless, homogenous masses resembling hyalin excepting that they take a light blue stain. The outstanding fact about these sections is the large amount of lutean tissue and the increased numbers of atretic follicles.

From series II the sections of the ovaries show lutean cells which are arranged in the typical cell-cord manner. There were no normal follicles. The inner granulosa cells are all proliferating. In some of the larger

follicles there was evidence of degeneration in the ova toward which the lutean cells were growing. The tunica was intact but the germinal epithelium has undergone hyperplasia, as shown by the many mitotic figures, and has grown downward into the ovarian stroma.

The sections of the ovaries of Series III appeared to be normal. The follicles present were normal in number and histological structure, there being no evidence of degeneration or other atretic changes. The corpora lutea present appeared to be normal in size and structure.

The histological findings in the ovaries of the rats receiving liver extract indicate that there may be changes due to the injected proteins. The ovaries of two of the rats appeared normal microscopically, but in three of the rats there was evidence of toxic action. One of the ovarian sections showed numerous large corpora lutea nearly replacing the ovarian stroma, with an apparent diminution in the number of follicles. Another one of the ovaries exhibited abnormal proliferation of the germinal epithelium. Atresia was rather evident in one of the other ovaries.

Our findings in these ovarian sections of the rats injected with pituitary exaract are very similar to those of Evans. There was a decided stimulation of lutean cells and imprisonment of the ova by lutean tissue as described by this investigator. The degeneration of the follicles in these rats was very marked. This degeneration of the follicles must lead to an inhibition of ovulation. There must have been some inhibition of ovulation because but few of the rats in series I became pregnant. The rats in series II also became pregnant later than those in series IV and V. The ovaries of the rats in series III did not seem to be affected by the injections and consequently, pregnancy was not deferred as much as in the two previous groups. The deferring of pregnancy was greater in group I than in the other two groups. The degeneration of the ovaries in this group was greater than in the other two groups. Our results are not in agreement with those of Putnam, Teel and Benedict (1928), who claim that acid extracts have little or no activity. We have observed the same retardation of pregnancy and ovarian changes that have been described by Evans and confirmed by Bellerby (1928).

Since Oslund (1926) has shown that protein injections may lead to degeneration of the seminiferous tissue, we thought protein injections intraperitoneally might cause some changes in the ovary. The oestrus cycles of the five rats which were injected with liver protein were normal compared with the results of Long and Evans (1922). The length of the oestrus cycles in these rats was the same as the control group of six rats. Though these results are not as decided as those reported by Evans we feel that they should not be overlooked. Since the protein content of his extracts was not determined we are not certain that we were injecting equivalent amounts of proteins. But in no case was the oestrus cycle retarded, even if there were evidences of ovarian injury. That oestrus may not be dependent on the follicles is stated by Parkes (1927), who sterilized mice by means of the x-ray. Such animals still had normal oestrus cycles.

This author believes that the synchronization of ovulation and oestrus is probably due to a common stimulus.

The testes of the rats receiving injections show active spermatogenesis but there was more than the normal amount of degeneration of the germ cells, especially of the intermediate stages of spermatogenesis, i.e., the spermatocytes. The sustentacular and interstitial cells were normal in number and structure. The testes of series IV and V were normal in every respect.

The weights of the testes of the rats receiving injections were less than those of the controls. This may, however, be attributed to the lower weights of these rats. This is not attributed to any specific effect of the pituitary extract but may be due to the proteins injected as Oslund (1926) has shown that injections of this type may lead to degeneration of the seminiferous tissue. From his results as well as our own we feel that the result may be a protein effect and not specific for any tissue extract. This degeneration of spermatic cells was, of course, not marked, as the females in these cages became pregnant. The weights of the testes of the normal rats compare favorably with weights according to Donaldson (1924) but the testes of the injected rats are definitely below the normal weight.

The results reported in this paper cannot be due to diet, nor any other factors than the injections. The coats of the animals were sleek and they appeared to be healthy in every way. The diets were evidently adequate in both sets of experiments because the weights of the controls were always above the normal. The reproduction and oestrus cycles of the animals not subjected to the injections were normal.

SUMMARY.

1. Albino rats injected intraperitoneally with acetic acid and alcoholic extracts of the anterior lobe of beef pituitary glands did not show any more rapid growth than the controls.

2. A substance or substances having a toxic action on ovarian follicles is present in the anterior pituitary gland extracts as prepared.

3. This toxic material is soluble in 50 per cent alcohol.

4. The toxic action exerted upon ovarian follicles by intraperitoneal injections may be due to the protein content.

5. Some degeneration in the ovary does not increase the length of oestrus cycle in the rat.

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DEMENTIA PRECOX AS AN ENDOCRINOPATHY WITH CLINICAL AND AUTOPSY REPORTS*

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LITERATURE

The literature contains many references to the changes of the endocrine glands in dementia precox. Kraepelin (1) in 1881 first called attention to the relation of this disease to the endocrines, especially to the sex glands.

Dercum (2) postulates that in dementia precox the various glands of internal secretion have suffered in the course of the development of the organism so that their respective functions are subsequently imperfectly and aberrantly performed. He feels that it is not at all unlikely that, while a number of glands, perhaps the entire chain, are involved in most cases, e.g., the gonads may dominate the picture, in others again it is the thymus; in still others it is the system of the pituitary, thyroid and adrenals. He regards the thymus as most likely to be involved because cases of dementia precox frequently betray in childhood the forerunners of the affection.

From the histological study of two cases Kojima (3) concludes that the thyroids have an opposite appearance in the male and female; a tendency to hypofunction in the male and hyperfunction in the female. He states that in dementia precox the glands, on the whole, are small, especially in the female. In the male the parathyroids contain watery, clear cells and a few eosinophile cells, and in the female on the contrary many eosinophile cells. The sexual glands and adrenals are small in the female. Striking changes are seen in the sexual glands, i.e., very slight spermatogenesis in the testes and an appearance of early involution of the ovaries.

Fränkel (4) found the infantile type of genitalia in 72 per cent of 176 cases of dementia precox cases examined, and Mott (5) showed pathologic changes in the testes and semen, defective maturation of the primordial follicles, degeneration of the nucleus and proliferation of the stroma, so that he believed that dementia precox results from deficient productive energy of the generative organs, based on congenital insufficiency of the gonads. He found a primary regressive atrophy in 27 cases of dementia precox in which the testes were examined.

Pézard (6) states that apparently the testes in the schizophrenic cease growing about the age of puberty, or soon after, thus allowing sufficient time in most cases for secondary sexual characteristics to develop, although

*Work done at the Blackburn Laboratory, St. Elizabeth's Hospital, Washington, D. C., and paper read before the Washington Clinico-Psychopathological Society, March 19, 1928.

these are always fully determined. Pézard in experimenting on the gonads of fowls, found that as little as a thirtieth of the testicular tissue left in the body permits development of the secondary sexual characteristics.

Matsumato (7) in a study of the relation between the reproductive organs and dementia precox, and Lewis (8) after a careful review of the autopsies of 143 cases of this disease as compared to 458 other autopsies, concludes that gonadal atrophy is more commonly found in dementia precox cases than in other individuals. Also, that in these cases the adrenal cortex as a whole is thinned out and pale in color. The zona glomerulosa is rudimentary and sclerotic, and the zona fasiculata shows acinal and cellular alterations. Unfortunately most of the authors take the degree of spermatogenesis as the criterion of degeneration of the endocrine function of the testes, which is an erroneous basis, as will be later pointed out.

Morse (9) studied 12 male and 15 females schizophrenics dying under 45 years of age, and concluded that 16 patients had active gonads. She used as criteria the presence of spermatogenesis and maturing follicles and corpora lutea. She states that there was no correlation between atrophy of the sex glands and the duration of the mental disease or the degree of psychic deterioration. The conditions in the sex glands of the controls were essentially the same as in the dementia precox cases for the same terminal diseases. The pituitaries in nearly half the cases presented a fibrosis, which could be correlated to some extent with similar condition in the gonads. This fibrosis of the pituitary is not peculiar to dementia precox but depends rather on the nature and the duration of the terminal disease. She states that the lesions in the adrenals were such as are usually found in the diseases to which the patients succumbed. The thyroid showed changes less frequently than the other endocrines. There was occasionally a mild, glandular hyperplasia or increase of connective tissue. From the pathologic side Morse feels that there is very little evidence of primary atrophy of the gonads in dementia precox, with the possible exception of those cases developing on a basis of mental defect.

Geller (10) attempted to show the close relations between the body and psyche in dementia precox on the basis of sexual function. He found considerable anatomic and functional hypogenitalism in 7 of 8 cases of dementia precox in women, and agrees with Mott, Frenkel, Hauck and Kohler that the disorder is intimately associated with deficient genital function. Serologic tests in these cases were found by Geller to show destruction of the brain, testes, ovary and often also of the thyroid substrates more frequently than in other psychoses. In 26 women his most important finding was that at the age of sexual maturity the genital organs were hypoplastic. Thus he feels justified in assuming a connection between inferior ovarian function and dementia precox.

Tsubura (11) in 1923 reported that individuals without gonads showed a lowered tolerance for sugar, and that if these individuals were given subcutaneous injections of either adrenalin or pituitrin, a marked hyper-

glycemia followed. He also found that if gonads were transplanted into these individuals, the above conditions were eliminated.

Benon (12) concluded that schizophrenia can be considered as a dementia, but should be regarded as a dysthymia, due to causes outside the brain.

Walker (13) states that the pituitary and adrenals are most important in the determination of the sex characteristics, and that the interstitial cells of the gonads are trophic rather than secretory. The following year Korenshevsky (14) reported that 60 per cent of castrated individuals become obese, while the remaining 40 per cent are usually thin. He found that in these cases the nitrogen metabolism is decreased. Lipschütz (15) states that the morphological and physiological changes which follow absence or deficiency of the gonads vary according to the age at which the deficit arose. He found that the thyroid of the hypogonad subject was usually small and that the hypophysis was larger and heavier than in normal individuals.

In order to prove whether the ovaries play a part in dementia precox, Pötzl and Wagner (16) removed the adnexa in two cases of long standing. Fibrosis such as described by Frankel in the testes of male schizophrenics was found in the ovaries. Hypothetically, a delay in the retrogression of the corpora lutea may be assumed as a manifestation of injury to the genital glands in female schizophrenics, they state, which is to a certain extent comparable to a pregnancy action. These workers had no favorable results from castration combined with homioplastic ovarian grafts in schizophrenic women. They attribute the menstrual aggravation to increased permeability of the meninges during these periods.

According to Sippel (17) a more or less pronounced hypoplasia and hypofunction of the sex glands is found in a considerable percentage of dementia precox cases. In a few cases he tried transplantation of ovaries in treatment of schizophrenia. In one case he obtained no results. Three subjects improved to a surprising extent.

Gibbs (18) found that some disturbance of lipoid metabolism may occur in dementia precox and may involve the suprarenal cortex as suggested by the following: (a) Previous observations on the sexual development and behavior of these patients; (b) the evidence that the suprarenal cortex is involved in these disturbances of sexual development; (c) the evidence that the suprarenal has both an embryologic and functional relation to the gonads on the one hand and to the brain on the other; (d) substances of a lipoid nature play an essential part in the functional metabolism of each of these organs; (e) the female sex hormone and the vitamine for reproduction are both of a lipoid nature; (f) the low basal metabolism rate frequently observed in dementia precox suggests an involvement of the suprarenals. He also found that in many patients with dementia precox the blood cholesterol was unusually low, and may be more directly

correlated with the psychosis and with sex than with any other recognized factor.

Münzer (19) describes in detail the case of a man of 25 years who quite suddenly developed a schizophrenic state with delusions, chiefly in the sexual sphere, and after three months committed suicide. The chief gross changes at autopsy consisted of enlargement of the thymus, which weighed 50 grams and showed marked increase in the number and size of Hassall's corpuscles; enlargement of the spleen and of the lymph follicles of the tongue and small intestines. The testes weighed 32 grams and showed marked atrophy and degeneration and abundant Lubarsch-Charcot crystals. The adrenals weighed 17 grams, with rather hypertrophic cortex and persistent undifferentiated cells of the zona glomerulosa of the cortex. There was reduction of the islands of the pancreas, and the thyroid presented a polymorphic picture, with good evidence of function, even hyperfunction, but also degenerated foci resembling those seen in idiots and cretins. One of the parathyroids lay within the thyroid; there was diminution of eosinophile cells, and on the whole these glands had preserved the characters seen in children. There was apparent increase in the eosinophilic cells in the hypophysis and an adenoma-like formation. Münzer maintains that abnormalities of the endocrines are constant in this psychosis.

The most complete recent study of the problem is by Langfeldt (20), who reports a detailed clinical examination of 40 unquestionable cases of dementia precox. He used every known diagnostic test of any value. His cases fell into three groups: 16 catatonic, 11 hebephrenic, and 13 mixed. In the catatonic group he found the following essential disturbances present in both the acute and the quiescent cases: slow pulse, low blood pressure, lymphocytosis, glandular swelling, positive pilocarpin test, positive Aschner reflex (vagotonic signs), and reduced basal metabolism. In the acute cases he noted also certain sympathicus signs such as dilated pupils, tachycardia, exophthalmos, and reduced glucose tolerance. In the hebephrenic cases, in the acute as well as the chronic phases, only sympathicus symptoms were found: tachycardia, exophthalmos, tremor, dilated pupils, and reduced glucose tolerance. These symptoms were, however, found most pronounced in the acute phases. In hebephrenia he found a normal basal metabolism and normal blood picture, apart from eosinopenia in the acute phases. In the hebephrenics he also found large firm testes.

Bowman (21) studied 24 cases of schizophrenia, both male and female, and found an abnormally low basal metabolism in 50 per cent, with a tendency to low or minus reading in nearly all the rest of the cases. Nearly one-half showed an abnormal blood sugar curve, all but one being of the "sustained" type. Over one-third showed a positive galactose test. X-ray studies and gastric analyses showed a definite functional disorder of the gastro-intestinal tract in about half of the cases and questionable functional disorders in all but two of the others. Radioscopy revealed

infected teeth in 40 per cent and questionable infection in 10 per cent more; "dropped" hearts in 30 per cent; questionable pulmonary tuberculosis in 13 per cent and healed pulmonary tuberculosis in 4 per cent more. The ovaries had been removed in several, and a number gave histories of severe illness in childhood.

EUNUCHS AND SCHIZOPHRENIA

While in China during 1925-27 I had opportunity to examine twenty Chinese eunuchs abandoned after the dissolution of the Imperial Court in Peking, and three Skopecs driven from Russia and taking refuge in China. The former type of eunuchs have been known in China as long as history, and were used as servants in the Imperial Palace. Many of these were castrated in youth, and were completely deprived of external genitals (23). The Skopecs were castrated because of their religious teachings and it is said that there were at least 150,000 members of this sect before the intolerance of the Soviet scattered them out of Siberia. This sect has been in existence since 1757, and many of the subjects were castrated in childhood. Two of the Skopecs examined had their external genitals completely removed, while the third had only been castrated. Female members of this religion may be only spayed, or their breasts may also be removed. Unfortunately for this record, no female Skopecs were seen in China.

All of the twenty-three eunuchs examined showed certain general characteristics. Fifteen tended to be obese and 8 were emaciated, probably due to starvation. The larynx was infantile. The extremities were proportionately larger than normal. In all cases it was found that the body height: leg length ratio was 1.75, whereas in an equal number of normal individuals it was 2.0. The pelvis was juvenile. There was an acrocynosis and the nails were spotted. Several showed a rather general cyanosis of the body, while the remainder were very pale. The skin was clammy, rather puffy, doughy, and creased. The subcutaneous fat in the gluteal region, under the breasts, in the trochanters, abdominal wall, and especially under the mons veneris, was more abundant than in normal men. The middle of the upper lip, the submental skin, the cheeks and the upper part of the neck were hairless. The perineum, axillae, and extremities did not have the abundant hair that is commonly found in the normal male. The pubic hair line was horizontal, or, in 2 or 3 of the individuals, concave.

Psychologically these individuals were found to all have good intelligence, were all orientated, but had been living a hand-to-mouth existence since they had been thrown on their own resources. They all appeared very introspective and apathetic. Although they could talk quite intelligently when questioned, they never volunteered any information, and appeared very stupid. They seemed methodical in their actions, and only two showed any purposeful efforts. There was a distinct lack of affect;

they were cold and passive, although in dire straits financially. At least half of the eunuchs had got into trouble because of their tempers, and two had been sentenced because of murder. They all appeared moody. Most of the eunuchs who still retained the penis stated that they had often indulged in sexual intercourse with prostitutes, although they had found that their erections were always of short duration. They all said that they indulged in homosexual practices and other perversions. Ten of them had had gonorrhea and one had an active chancre. Unfortunately no blood examinations or basal metabolism tests could be made on these subjects, but Shen and Lin (24) have reported the nitrogen metabolism of eunuchs examined by them, and it conforms to the general picture.

Because the examination of these eunuchs showed them to be almost typical prototypes of what is considered "dementia precox," it was decided to make an examination of the autopsy material of diagnosed "dementia precox" cases recorded at Saint Elizabeth's Hospital, and to examine a large number of "dementia precox" patients under care at the Government hospital for mental diseases, and to see if the symptom-picture remained constant.

CLINICAL EXAMINATION

In order to determine a normal somatic standard, 50 normally reacting males and 24 normally reacting females between the ages of 16 and 50 years were first examined. The individuals were seen during the routine examination for life insurance and could all be classed as normal healthy individuals.

In selecting the patients the various services at the hospital, which cares for 3960 psychopaths, were asked for a list of cases considered without doubt to be typical examples of "dementia precox," and 70 of these males and 40 female cases were given careful physical examinations.

Males

The males ranged between the ages of 18 and 48 years, but 77.1 per cent were under 30 years of age and all appeared in good physical health. Of this number, 38.8 per cent were of the thin type, and 27.7 per cent were obese. Five and a half per cent showed acrocynosis and most of them appeared rather pasty; 11.1 per cent had polyuria, 5.5 per cent increased salivation, and 5.5 per cent showed dermographism.

Sixty per cent were found to have female distribution of hair, 38.5 per cent had a penis smaller than normal, while 22.8 per cent had a penis larger than normal. Only 5.7 per cent had apparently normal testes, all the rest being smaller, larger, softer, harder, etc., than normal; 68.5 per cent showed more or less disease of the prostate. Forty per cent were circumcised or had a retracted prepuce.

Of the five married patients, three had children, totaling eight in number. Two of the single patients definitely knew they had had chil-

dren. Of all the patients, 43 per cent showed unmistakable signs of masturbation; 5 of the men had undoubtedly abused themselves to excess, while 2 had questionably indulged in this practice. About 50 per cent had occasionally had coitus before coming to the hospital, and 50 per cent continued to have an occasional orgasm with extrusion of semen, either mechanically or during erotic dreams. About 7 per cent had very infrequent orgasm, while 8.5 per cent had one or more orgasms daily while in the hospital. Only 20 per cent said they had desire for heterosexual practices.

At least 40 per cent of the patients had a history of gonorrhea and 10 per cent had a history of syphilis. Over 22 per cent had had a severe toxic illness before the onset of the psychosis. The severe attacks recorded were diphtheria, yellow fever, malaria, small-pox, mumps, scarlet fever, and influenza. Of all the patients, 5.5 per cent had been known as "weak children"; an equal number had one psychopathic parent; another 5.5 per cent had been heavy drinkers before the onset of the psychosis.

There is plenty of authority to substantiate the fact that the toxemias have a very deleterious effect on the endocrines, and some, such as mumps, appear to have a selective effect on the gonads. The adrenals are known to be especially sensitive to toxins.

The fact that a person is able to have an erection or even to have an orgasm is no criterion of the endocrine state of his testes. Erection may not be associated with sexual desire, for priapism may be a sign of cervical injury, myeloid leukemia or tabes, even though the testes have been removed. Then, again, the reflex centers may have acquired the mechanism of erection before the loss of the sexual stimulation, as was shown by the foregoing report concerning eunuchs. As to extrusion of semen, this may take place without erection, simply as a reflex emptying of distended vesicles.

From the reports concerning the Mujerados of Mexico it may be concluded that excessive extrusion of semen causes atrophy of the gonads. These individuals, descendants of the Aztecs, are masturbated to orgasm several times daily until testicular degeneration takes place. These men become virtually eunuchs and acquire the characteristics of the latter. They are used as menial servants. It is possible that the history of sexual excess in the schizophrenics examined may account for some of the gonadal dystrophy found, although, as will be later shown, the moderate practice of masturbation is conducive to continuation of spermatogenesis.

Females

The female patients examined ranged between 16 and 47 years of age, but 87.5 per cent were between 20 and 40. The onset of the first signs of psychosis was recorded as being between 10 and 18 years of age in most of the cases. Seventy-five per cent of the women were married.

The majority were of the thin type; 22.5 per cent showed male distribution of hair; 7.5 per cent had hypertrophied external genitals; 12.5 per cent had large pendulous breasts; 17.5 per cent small infantile breasts; 10 per cent, flat breasts; 2.5 per cent had normal appearing breasts but after pregnancy did not lactate; 7.5 per cent had extremely large breasts.

Fifty per cent had amenorrhea, 14.3 per cent vicarious menses, 14.3 per cent profuse menses, 7 per cent irregular periods, 28.5 per cent dysmenorrhea, and 7 per cent scanty menses. Thirty-five per cent had been pregnant one or more times, 25 per cent had had miscarriages, and 12.5 per cent had normal births; 5 of the women had 11 children. Of all the subjects, 7.5 per cent were distinctly homosexual, 2.5 per cent had excessive sex desire, and an equal number had had precocious sex development.

On bimanual examination and from past history of operations it was found that 52.5 per cent of the women had unmistakable ovarian disease, 42.5 per cent had uterine trouble, 25 per cent had had ovariotomies, and 2.5 per cent showed infantile uteri. Five per cent showed first signs of psychosis during pregnancy and 2.5 per cent showed definite venereal infection.

Fifty-five per cent of the patients had had serious illness before psychopathic symptoms: 27.2 per cent of this number had a severe attack of measles: 27.2 per cent, scarlet fever; 18 per cent, malaria; 18 per cent, pertussis; 13.6 per cent, diphtheria; 9 per cent, mumps; 9 per cent, typhoid; 4 per cent, influenza; 4 per cent, pneumonia; 4 per cent, inflammatory rheumatism; 9 per cent, peritonitis; 27.2 per cent had been undersized or delicate as children.

AUTOPSY STUDIES

A detailed study of 487 autopsies was made to determine if there were any biometric and microscopic differences between the cases diagnosed as *dementia precox* and the other psychoses. Of this number, there were 158 male (between the ages of 19 and 97), and 24 female (between the ages of 21 and 85), "dementia precox" cadavers, and 241 male (between the ages of 21 and 97), and 64 female (between the ages of 15 and 86), cadavers dying at Saint Elizabeth's Hospital without the diagnosis of "dementia precox."

All the cases were divided into age groups: 20 to 30, 30 to 40, 40 to 50, 50 to 60, 60 to 70, and all over 70 years. The cases with the diagnosis of "dementia precox" were separated into catatonics, hebephrenics, and mixed. The last group included all those diagnosed paranoid, simple, or undifferentiated.

Male Autopsies

The males examined in the schizophrenic group ranged in age from 19 to 97 years; 11 per cent were between 20 and 30, 18 per cent between 30 and 40, 20 per cent between 40 and 50, 18 per cent between 50 and 60, 17 per cent between 60 and 70, and 16 per cent over 70 years old. None of the catatonics were over 50 years of age. The dementia precox patients had been in the hospital from 6 months to 54 years; their records showed the onset of insanity to be anywhere from 18 to 55 years of age. Of these cases 24.5 per cent were of the catatonic type; 39.5 per cent, hebephrenic; and 36 per cent, mixed.

Tuberculosis in some form was responsible for the death of 39.9 per cent of the schizophrenics, while it was the cause of death of only 8.3 per cent of the other psychotics. Pneumonia caused the death of 27.7 per cent of the dementia precox, and 56 per cent of the other subjects. Myocarditis was the lethal disease in 12.3 per cent of the schizophrenics and 35 per cent of the others. All the category of

diseases could be found in the other cases not included in the above percentage, although 67 per cent of the dementia precox subjects showed myocardial degeneration.

Of the schizophrenic males, 51.25 per cent were thin; only 10 per cent were obese; the remaining 38.75 per cent were within normal limits of weight.

Eighty per cent of the schizophrenics showed female hair distribution; 42.5 per cent were circumcised or had retracted prepuces; 62.5 per cent showed obvious signs of masturbation.

The brain in 31.1 per cent of the schizophrenics was found to be normal in all respects, while only acute or minor degenerative changes were found in the remaining 68 per cent. The meninges appeared thinner than the average in 55.5 per cent of the brains. The 20 to 30 year dementia precox group showed an average brain weight of 1314 grams as compared to 1281 grams in the other psychotics; from 30 to 40 years, 1263 grams as compared to 1276 grams; 40 to 50 years, 1328 grams as to 1284 grams; 50 to 60 years, 1393 grams as to 1260 grams; 60 to 70 years, 1236 grams as to 1241 grams; and over 70 years, 1213 as to 1170 grams.

The hypophysis was normal in 42 per cent of the dementia precox autopsies, 38 per cent were atrophic or sclerotic, 5.2 per cent cystic, and only one was hyperplastic. This gland in the 20 to 30 year group gave an average weight of 605 mgm. as compared to 725 mgm. for the non-schizophrenic individuals; 30 to 40 years, 691 as to 698 mgm.; 40 to 50 years, 737 as to 681 mgm.; 50 to 60 years, 634 as to 667 mgm..; 60 to 70 years, 660 as to 655 mgm.; and over 70 years, 623 as to 606 mgm. The schizophrenic glands showed an average cell content of 43 per cent eosinophiles, 17 per cent basophiles, and 40 per cent neutrophiles, with 20 per cent of the glands showing the relation 55-10-35, and an equal number, 35-10-55, with 16 per cent showing 30-20-50. The non-schizophrenic glands gave an average of 52 per cent eosinophiles, 28 per cent basophiles, and 20 per cent neutrophiles, with 24 per cent of the glands giving the relation 45-35-20; 20 per cent giving 60-20-20; 16 per cent 70-15-15; and 12 per cent 30-50-20.

The pineal was found to be normal in all respects in 46 per cent of the dementia precox cases, while 38 per cent showed an atrophic, sclerotic, or fibrosed gland. Biometrically there was nothing to be noted.

The thymus showed fatty degeneration in 54 per cent of the dementia precox cases. This gland in the 20 to 30 year old individuals gave an average weight of 8.4 grams with 17.1 per cent active tissue present, as compared to 14.4 grams and 40 per cent activity in the non-schizophrenic cases of this age; 30 to 40 years showed 8.68 grams and 15 per cent activity as compared to 10.5 grams and 24.6 per cent; 40 to 50 years, 10.8 grams and 11.9 per cent as to 11.25 grams and 7.5 per cent; 50 to 60 years, 19.5 grams and 12.7 per cent as to 19.7 grams and 2.4 per cent; 60 to 70 years, 18.19 grams and 2.27 per cent as to 26.18 grams and 6.54 per cent; and over 70 years, 11.5 grams and 1.56 per cent as compared to 12 grams and 3.7 per cent activity.

The thyroid was found to be normal in 39 per cent of the dementia precox cadavers, hypertrophied in 6 per cent, and atrophied or fibrosed in 43.2 per cent. Most of the normal glands were found in the catatonics. From 20 to 30 years the catatonics showed an average thyroid weight of 10.12 grams, hebephrenics 26.4 grams, mixed type 27 grams, with a general average of 19.3 grams as compared to 22.74 grams in the non-schizophrenic cases; 30 to 40 years, 20.8 grams, 18.6 grams, and 20.39 grams, respectively, with an average of 19.79 grams as to 24.14 grams; 40 to 50 years, 28.75 grams, 24.99 grams, 23.73 grams, respectively, with a general average of 25.2 grams as to 41.58 grams; 50 to 60 years, a general average of 19.33 grams as to 28.05 grams; 60 to 70 years, 23.22 grams as to 25.55 grams; and over 70 years, 22.76 grams as to 22.22 grams.

The parathyroid glands in 44 per cent of the dementia precox cases were found to be normal, 30 per cent showed fatty infiltration, and 26 per cent atrophy or fibrosis. The weight of these glands was not significant.

The pancreas showed nothing striking. Forty-four per cent of these glands found in the dementia precox cadavers were normal, 17 per cent showed fatty infiltration, 13 per cent fibrosis, and all the rest acute or autolytic changes.

The adrenal glands revealed some rather remarkable changes, as only 25.3 per cent of the glands could be classed as normal. One old schizophrenic 60 years of age had hypertrophy of the medulla, two others, 67 and 58 years of age, had hypertrophy of the cortex, and one subject, 30 years of age, who had the beginning of his psychosis when 27 years old with a diagnosis of hebephrenic type had hypertrophy of both the medulla and cortex, and a degeneration of the testes. The rest of the glands examined were atrophic. From 20 to 30 years, the cata-

tonics gave an average weight of 7.02 and 6.42 grams, respectively, for the right and left adrenals; the hebephrenics, 5.93 and 7.13 grams; mixed, 7.6 and 7.6 grams, with a general average of 6.81 and 6.87 grams as compared to 6.5 and 7.6 grams for the control cases. From 30 to 40 years the weights were 6.8 and 7.76 grams, 7.2 and 7.34 grams, 5.98 and 7.54 grams, with a general average of 6.67 and 7.51 grams as compared to 7.19 and 7.69 grams; 40 to 50 years, 6.13 and 6.53 grams, 7.7 and 8.85 grams, 6.7 and 7.33 grams, with a general average of 6.87 and 7.57 grams as to 7.41 and 7.74 grams; 50 to 60 years, a general average of 5.91 and 6.12 grams as to 7.06 and 7.95 grams; 60 to 70 years, 8.23 and 10.26 grams as to 6.06 and 7.03 grams.

The prostate was hypertrophied in slightly over 50 per cent of the dementia precox cases; 9 per cent were congested; 5.4 per cent atrophied; 14.5 per cent were normal.

The most interesting findings in the endocrine system of the dementia precox cadavers were seen in testes, in that only 4.4 per cent of these glands were normal and this small percentage might quite well be accounted for by the errors of psychological diagnosis. Thirty-four per cent of the testes were fibrosed and 61.6 per cent were diagnosed chronic interstitial orchitis. From 20 to 30 years the testes gave an average of 12.08 and 11.46 grams, respectively, for the right and left gonads in the catatonic group; 11.25 and 10.27 grams for the hebephrenic; 14 and 11.5 grams for the mixed cases; and a general average of 12.21 and 11.1 grams, with 42.6 per cent of the testes showing chronic interstitial orchitis, 42.6 per cent atrophy, and only 14.8 per cent were apparently normal; while the non-schizophrenic testes of this age gave 11.92 and 11.12 grams, respectively, and 80 per cent were normal while 20 per cent showed parenchymatous degeneration. From 30 to 40 years the catatonics gave a weight of 12.25 and 9.28 grams, the hebephrenics 10.99 and 9.94 grams, and the mixed 12.22 and 12.21 grams, with a general average of 11.76 and 10.59 grams, 40 per cent chronic interstitial orchitis, 30 per cent atrophy, 20 per cent fibrosis, and 10 per cent minor degenerative changes, as compared to 13.79 and 14.68 grams in the controls, 28 per cent of the glands showing chronic interstitial orchitis; 16 per cent, atrophy; 8 per cent, fibrosis; 4 per cent, parenchymatous degeneration; and 44 per cent being normal. From 40 to 50 years the findings were 12.55 and 13.38 grams, 12 and 11.24 grams, 14.08 and 13.56 grams, with a general average 13.16 and 12.86 grams, and 18.2 per cent chronic interstitial orchitis, 45.5 per cent atrophy, 36.6 per cent fibrosis, as compared to 15.2 and 14.2 grams, and 18.2 per cent chronic interstitial orchitis, 18.2 per cent fibrosis, 9 per cent atrophy, and 4.5 per cent parenchymatous degeneration. In the 50 to 60 year group there was a general average of 15.08 and 14.09 grams weight, and 55.6 per cent fibrosis, 22.3 per cent chronic interstitial orchitis, 11.1 per cent sclerosis, and 11.12 per cent atrophy, as compared to 14.98 and 13.26 grams and 33.3 per cent fibrosis, 16.7 per cent chronic interstitial orchitis, 16.7 per cent atrophy, and 33.4 per cent parenchymatous degeneration. In the 60 to 70 year group the findings were: 14.7 and 15.7 grams, with 25 per cent chronic interstitial orchitis, 50 per cent atrophy, 12.5 per cent fibrosis, and 12.5 per cent parenchymatous degeneration, as compared to 13.1 and 12.8 grams, and 10 per cent chronic interstitial orchitis, 40 per cent atrophy, 30 per cent fibrosis, and 20 per cent parenchymatous degeneration in the controls. Over 70 years old, the glands showed 11.68 and 10.73 grams and 50 per cent atrophy, 40 per cent fibrosis, and 10 per cent chronic interstitial orchitis, as compared to 13 and 11.9 grams, and 50 per cent atrophy, 11.1 per cent fibrosis, 33.3 per cent chronic interstitial orchitis, and 5.6 per cent parenchymatous degeneration.

In studying the testes, as mentioned before, unfortunately pathologists have taken the presence or absence of active spermatogenesis as the criterion of functioning or non-functioning testes. The trend of the available evidence is to the effect that the incretion of the gland is mediated, not by the spermatogenic but by the lipoidal type of interstitial cells between the spermatic tubules. The presence or absence of this constituent is the true criterion of the endocrine activity. Spermatogenesis is dependent on sexual activity, although shrinkage of the interstitial substance may cause occlusion of the spermatic tubules and thus an atrophy. Subjects, whether of dementia precox or not, who indulged in moderate sexual stimulation, either by coitus or masturbation, showed active spermatogenesis in spite of age. Retention of the spermatozoa caused atrophy, and over stimulation appears to cause degeneration by fatigue. Testes of the control subjects, although in many cases containing no spermatozoa, still had varying amounts of interstitial elements, while masturbating or sexually active schizophrenics, although having apparently normal spermatogenesis, had testes containing little or none of the lipoidal substance.

Female Cadavers

Of the 24 female dementia precox cadavers examined, 20 per cent were of the catatonic type; 35 per cent, hebephrenic; and 45 per cent were mixed. Of all subjects, 58 per cent were legally married, 8 per cent had been in "free-love" marriage, and 34 per cent were single. All but two of the married women had children, having from 1 to 5 each, and one of the single women had had a miscarriage. The histories revealed that the psychoses developed between the ages 17 and 52 years, while about 80 per cent of the women developed their psychoses before 39 years of age.

Thirty per cent gave a history of a severe attack of measles some time in their lives; 20 per cent, scarlet fever; 10 per cent, typhoid; 10 per cent, diphtheria; 10 per cent, mumps; and 10 per cent, influenza; 10 per cent had had chorea, 30 per cent showed histories of alcoholism in one or both of the parents, 20 per cent had parents that were psychotic, 10 per cent had had miscarriages, and 30 per cent dated the psychosis from pregnancy. Only three subjects gave menstrual histories; one woman of 35 years, with grossly normal reproductive organs, had had amenorrhea for the last 4 years before death; another had had amenorrhea for 20 years before death, and another, of 34 years, had had irregular menses and dysmenorrhea all her life.

The primary cause of death in 25 per cent of the dementia precox women was myocarditis and another 25 per cent, pneumonia; 20 per cent had streptococcus septicemia, 15 per cent tuberculosis in some form, and 15 per cent carcinoma. Of the control psychotic group, 43 per cent died of myocarditis; 30 per cent, pneumonia; 13 per cent, neurosyphilis; 9 per cent, tuberculosis; and the remaining 5 per cent died of septicemia, encephalitis, etc.

Of the total number of females coming to autopsy, 21 per cent of the dementia precox and 6 per cent of the control subjects were between 20 and 30 years of age at death; 17 per cent and 8 per cent, respectively, between 30 and 40 years of age; 8 per cent and 8 per cent between 40 and 50 years; 21 per cent and 16 per cent between 50 and 60; 8 per cent and 19 per cent between 60 and 70; and 25 per cent and 43 per cent over 70 years of age. There were no catatonics over 50 years old.

As compared to 61 normal females, 45 per cent of the dementia precox cadavers were thin, 25 per cent were obese, 20 per cent higher, and 40 per cent shorter than normals of the same age, while of all the other female psychopaths coming to autopsy 52 per cent were thinner than normal, and 17 per cent were obese. Slightly over 14 per cent had scanty hair growth, while 28.5 per cent had male distribution of hair, 43.8 per cent had atrophic breasts, 6.2 per cent had juvenile breasts, and 43.8 per cent had pendulous mammae.

Forty-five per cent of the dementia precox subjects showed normal brains both macroscopically and microscopically, but 30 per cent had what appeared thinner meninges than normal, while 20 per cent had thicker than normal. The average brain weight of the schizophrenics between 20 and 30 was 1140.5 grams as compared to 982.5 grams for the non-dementia precox cases; 30 to 40 years, 1231.75 grams as compared to 1174.83 grams; 40 to 50 years, 1196.33 to 1063.4 grams; 50 to 60 years, 1187.5 to 1146.93 grams; 60 to 70 years, 1153 to 1104.25 grams; and over 70 years, 1023 grams as compared to 1131.97 grams.

In the dementia precox group, 37.5 per cent showed a normal hypophysis, 43.7 per cent an atrophic or fibrosed hypophysis, and 18.8 per cent acute congestion. This gland in the 20 to 30 years old schizophrenic group showed an average weight of 805 mgm. as compared to 670 mgm. in the general group; 30 to 40 years, 662.5 mgm. as compared to 768.33 mgm.; 40 to 50 years, 806.67 mgm. as to 786 mgm.; 50 to 60 years, 816.67 mgm. as to 855 mgm; 60 to 70 years, 680 mgm. as to 802.5 mgm.; and over 70 years, 657.67 mgm. as to 762.59 mgm. The cell content of the glands in the dementia precox cadavers showed an average of 52 per cent eosinophile cells, 21 per cent basophils, and 27 per cent neutrophils, with 29.4 per cent of the glands showing the relation 60-20-20; 17.7 per cent, 70-15-15, and a similar number, 30-10-60; and 15 per cent showing 30-30-40, as compared to the glands found in the non-dementia precox group, which showed an average of 57 per cent eosinophils, 20 per cent basophils, and 23 per cent neutrophils. Of these glands 29.4 per cent showed the relation 70-10-20; 17.7 per cent, 60-20-20; 15 per cent, 50-20-30; and a similar number, 40-50-10.

The pineal gland was normal in 46 per cent of the dementia precox group, and 38 per cent showed sclerosis.

The thymus glands from the dementia precox cadavers showed anything from 0 to 100 per cent active tissue, but only 20 per cent showed more than 25 per cent or more activity, while 57 per cent of the glands showed 5 per cent or less active

tissue present. This gland from the catatonics between 20 and 30 years of age on the average weighed 5 grams, and showed 20 per cent active tissue; from the hebephrenics, 1.2 grams and 70 per cent; while the mixed group showed 9.73 grams and 3 per cent, with an average of 6.73 grams and 24 per cent, as compared to the control cases, 7.33 grams and 63.3 per cent. The 30 to 40 year group showed 6.4 grams without active tissue; 5.9 grams with 5 per cent, and 4 grams without activity, respectively catatonic, hebephrenic, and mixed, with an average of 5.55 grams and 5 per cent, as compared to 12.11 grams and 39.33 per cent active tissue in the control group. From 40 to 50 years all of the dementia precox cases showed an average of 6.02 grams and 55 per cent as compared to 10 grams and 16.6 per cent in the others; from 50 to 60 years, 7.1 grams and 7 per cent as to 9.1 grams and 19.9 per cent; from 60 to 70 years, 16.1 grams and 0.5 per cent as to 12.25 grams and 1.5 per cent; and over 70 years, 6.62 grams and 2.4 per cent as compared to 9.48 grams and 2.14 per cent active tissue.

Forty per cent of the thyroids from the dementia precox cadavers were normal, 35 per cent were atrophic, 15 per cent showed thyroiditis, and 10 per cent were hypertrophied. The 20 to 30 group of catatonics showed an average weight for the thyroid of 13.15 grams, the hebephrenics 21.5 grams, the mixed 18.27 grams, with an average for the dementia precox cases of 17.27 grams, as compared to the control weight of 24.79 grams. From 30 to 40 years the weights were 18, 16.62, and 28.7 grams, with an average of 19.99 grams, as compared to 18.05; 40 to 50 years, 25.5 grams, and 25.85 grams for the catatonics and hebephrenics, respectively, with an average of 25.6 grams, compared to 18.18; 50 to 60 years showed an average for the dementia precox cases of 21.37 grams as compared to 23.17 grams; 60 to 70 years, 18.25 grams against 19.55 grams; and over 70 years 25.63 grams, compared to 19.65 grams.

The parathyroids in the dementia precox cases showed 40 per cent of the glands with marked fatty infiltration, 26.6 per cent atrophy or sclerosis, 6.6 per cent increase of the interstitial cells, 13.5 per cent congestion, while only 13.3 per cent of the glands were normal.

The pancreas was normal in 30 per cent of the cases; 50 per cent showed fatty infiltration and degenerative changes, and 20 per cent were diagnosed pancreatitits. Many of the pathological changes were probably due to acute toxic or autolytic catabolism.

Both the cortex and medulla of the adrenals were normal in only one case, a woman 39 years of age with the catatonic type of dementia precox. She weighed 35 kgms. and was 162 cm. in height. Ten per cent of the cases showed normal medullas and 5.3 per cent enlarged medullas. Forty-two per cent showed degenerative changes in the whole gland, 5.3 per cent, fatty infiltration; 10.5 per cent, cloudy swelling; 42 per cent, markedly narrow cortex; 10.5 per cent, hypertrophied cortex, and 5.3 per cent, edema of the cortex. The catatonics from 20 to 30 years of age showed an average weight of 6.75 grams and 7.35 grams, respectively, for the right and left glands; the hebephrenics, 7.8 and 7.5; the mixed, 6.2 and 6.13, with an average of 6.67 and 6.77 grams, as compared to 5.3 and 6.86 grams for the control group; from 30 to 40 years, 5.5 and 5, 5.65 and 7.05, 6.5 and 7.2, and an average of 5.83 and 6.58, as compared to 6.02 and 5.83 grams; from 40 to 50 years, 5.47 and 6.37, as compared to 5.18 and 6.26; from 50 to 60 years, 6.38 and 6.18, as compared to 6.91 and 7.77; from 60 to 70 years, 5.23 and 5.1, as to 6.37 and 7.51; over 70 years, 5.15 and 4.53, as to 5.79 and 6.24 grams.

The uterus was normal in only 15 per cent of the cases, while none of the ovaries were normal. Twenty-five per cent of the subjects had had their ovaries previously removed, while of the ovaries examined, 33.3 per cent were atrophic, 60 per cent were sclerotic or cystic and 6.3 per cent were cancerous. In the various age groups of control cases there were some changes in the ovaries, but nothing comparable to the general subnormality of the dementia precox gonads. From 20 to 30 years the average weight of the right and left ovaries was, respectively, 2.63 and 2.61 grams, as compared to 3.45 and 3.26 grams in the control cases, with only 25 per cent showing fibrosis; from 30 to 40 years, 3.4 and 4.2 grams as to 3.42 and 3.9 grams, with 20 per cent showing fibrosis and 20 per cent more showing other regressive changes; 40 to 50 years, 2.65 and 3.7 grams as to 3.51 and 3.26 grams, with 40 per cent showing atrophic changes; 50 to 60 years, 1.77 and 1.6 grams as to 6.42 and 4.15 grams, with 50 per cent showing atrophy, fibrosis, or cyst formation; 60 to 70 years, 1.4 and 1.45 grams as to 1.98 and 1.87 grams, with 42 per cent atrophic; and over 70 years of age, 1.87 and 1.7 grams as to 2.41 and 2.61 grams, with 58 per cent atrophic or sclerotic, and the remaining 42 per cent showing the normal regressive senile changes.

DISCUSSION

Dementia precox in the past has been more or less placed in the class of incurable and hopeless diseases, and anything that offers a possible amelioration is worthy of support. Much suggestive work on the problem has been done in the past, but without proper cooperation and without being brought to a satisfactory conclusion.

The clinical and histo-pathological work that has already been completed shows that there is apparently no constant alteration in the brain substance, but a very consistent lack of gonadal incretion. Examination of eunuchs shows them to have schizophrenic characteristics with marked affect disorganization, while, on the other hand, unmistakable subjects of dementia precox are quite consistently eunuchoid in physique.

The castrated man or woman tends more or less towards a common type, that is, a juvenile form common to both sexes, or to a form in which, as in the intrauterine stage, sexual divergence has not yet taken place. In the ontogenetic development of the soma there is an asexual stage. The asexuality that for various reasons apparently develops to form the dementia precox symptom-complex is a very logical explanation for the familiar regression found in dementia precox.

It is well known that the endocrines are very sensitive to toxins, such as those of mumps and scarlet fever, as well as alcohol or opium, causing ovaritis or orchitis. There is abundant pathological evidence to show that patients dying in acute toxemia have hemorrhagic and destructive changes in the adrenals. Patients seldom recover from typhoid without some endocrine imbalance. Thus a history of toxemia or fatigue, either prenatal or postnatal, is suggestive as a precursor of dementia precox. The tenseness of catatonia might be explained by the apparent hyperfunction of the thyroid in these cases.

Without the driving force desired from the endocrines and, especially, the gonads, there is no wonder that the so-called dementia precox character develops.

If it be true that this disease is primarily a disorder of the endocrine system, and especially of the gonads, the supplying of this incretion should assist the individual in readjustment to life. It is hoped that in due time this will be proved.

SUMMARY AND CONCLUSIONS

The literature, in general, supports the contention that endocrinopathy is consistently found in dementia precox cases.

Twenty-three eunuchs examined by me showed typical dementia precox or schizoid character—good intelligence and orientation, but distinct changes in the affect. Some retained sexual function but without libido.

Seventy living schizophrenic males examined showed at least 60 per cent to be eunuchoid in type and only 5.7 per cent having apparently nor-

mal testes, with also other signs of endocrine dysfunction. A large number functioned sexually.

Of forty living female subjects of dementia precox, 52.5 per cent had undoubted ovarian disease, although some had been able to be pregnant.

Pathological examination of 158 male and 24 female schizophrenics disclosed marked endocrine changes. No catatonic cadavers over 50 years of age were seen. No consistent pathological or biometric changes were found in the endocrines except in the gonads, although only a small percentage of the subjects had normal adrenals. The thyroid was consistently normal or hypertrophied in all cases of catatonic dementia precox. In the dementia precox cases no normal ovaries and only a small percentage of normal testes were found. The male dementia precox subjects of the catatonic type showed an average weight of 13.17 and 12.47 grams, respectively, for the right and left testes; the hebephrenic, 11.47 and 11.40 grams; and the mixed, 13.61 and 12.90 grams; with a general average for all the dementia precox males of 13.26 and 12.85 grams, as compared to 13.84 and 13.66 grams for the control psychotic group. The female dementia precox subjects showed an average weight of 3.6 and 3.3 grams, respectively, for the right and left ovaries, in the catatonics; 3.28 and 3.17 grams in the hebephrenics; 2.01 and 1.88 grams in the mixed group; with a general average of 2.96 and 2.75 grams, as compared to 3.28 and 2.85 grams for the control females.

Tuberculosis was the lethal disease in 39.9 per cent of the men but in only 15 per cent of the women. Myocardial degeneration was consistently present in a large percentage of both the male and female dementia precox cases, and pneumonia was a very frequent cause of death in both sexes. Almost every dementia precox individual gave a history of having had one or more of the severe toxemias. At least a fourth of the subjects had inherited defective somatoplasm.

This study as a whole indicates that dementia precox is primarily an endocrinopathy in which the gonads are consistently degenerated or hypofunctioning.

Sexual activity and fecundity are no adequate criteria of gonad incretion, but rather the state of the interstitial lipoid should be taken as the criterion of normality.

Supplying of the endocrine deficiency should assist in the social adjustment of the victims of dementia precox.

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THE ORAL ADMINISTRATION OF ADRENALIN

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That adrenalin is ineffective when administered by mouth seems to be an accepted fact. That it is destroyed by the gastric and intestinal juice is the general belief. Systemic effects from oral administration are thus questionable.

Menninger (1927) states that only large doses of adrenalin, when given by mouth, have any effects on the blood pressure of experimental animals. He quotes Herter and Wakeman (1902) as attributing no effects, when adrenalin was given in "ordinary" doses. No effects were produced in a well-fed dog weighing 13 kgm. when 10 cc. of 1-1000 was administered. A one per cent glycosuria was produced in a dog, over a short period of time, without other symptoms, when 30 cc. of 1-1000 was given. Falta and Ivacovic (1909) found that even 20 mgm. or more per day did not produce any special manifestations in dogs.

Dorlencourt, Trias, and Paychere (1922) obtained only hyperglycemia and never any changes in blood pressure. They administered large doses and concluded from their results that adrenalin passes through the portal system to the liver, where it is destroyed. They used chloralose as an anesthetic, under the assumption (warranted by the results of their own observations) that it would not increase the blood sugar.

After reviewing clinical and other observations, Menninger (1927) comes to the conclusion that the results are inconsistent and unreliable. It was therefore suggested to us by Professor T. C. Burnett that the experiments should be repeated without anesthesia, thus eliminating the possibility of hyperglycemia from the chloralose.

EXPERIMENTAL

1. *The effects of adrenalin on the blood sugar of dogs, when administered by stomach tube.*

Only dogs in the post-absorptive state were used. The animals were trained to remain quiet throughout the experiments, while strapped to a dog board, with the stomach tube in place. Blood was drawn from the femoral artery. A normal sample was taken and 10 cc. of 1-1000 adrenalin in 40 cc. of water administered by stomach tube and washed down with 10 cc. of water. Immediately following the administration of adrenalin another sample of blood was drawn in order to check up any possible

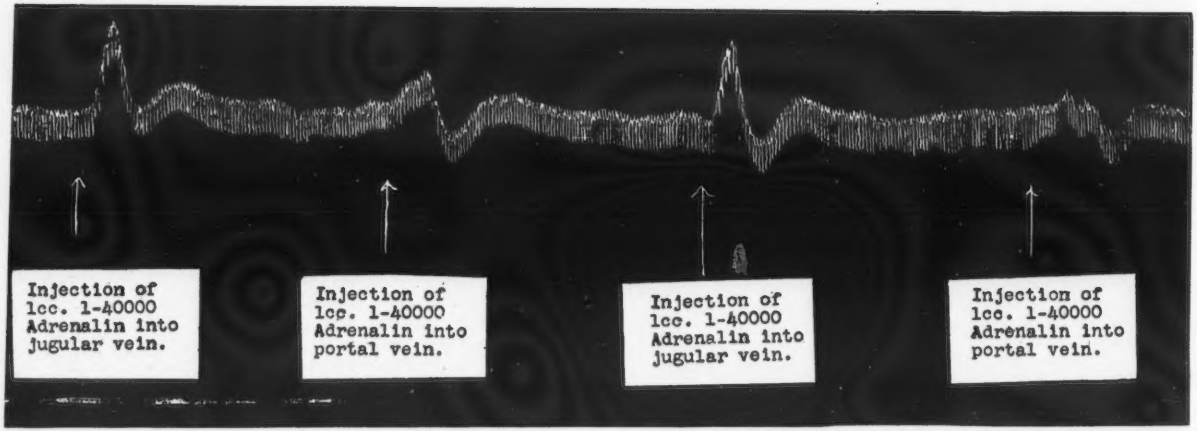
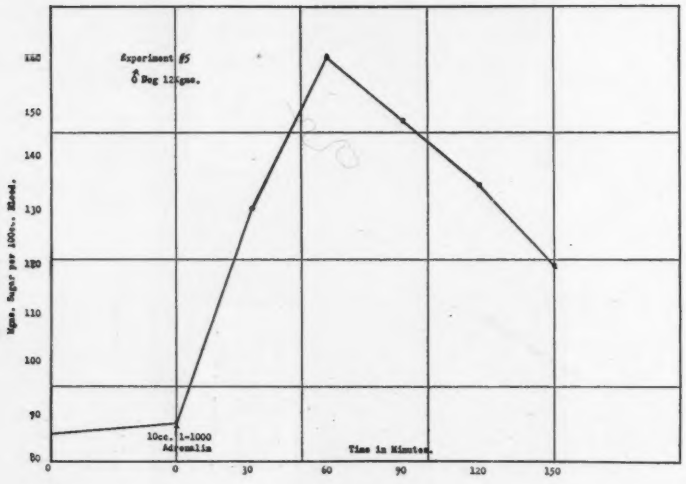


Fig. 1. Injection of 1cc. 1-40,000 Adrenalin into jugular vein followed by a similar injection into portal vein.



Animal	Before Administration of Adrenalin	Immediately Following Adrenalin	Time in Minutes After Administration of Adrenalin				
			30	60	90	120	150
	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.	mgm.
1 10 kgm. control	96.1	95.2	97	97.5	98	98	95
2 10 kgm.	99	101	130	151	135	123	118
3 10 kgm.	96	95 6	128	165		137	129
4 12 kgm. control	86	88.2	85	87	87	86 5	88
5 12 kgm.	86	87.3	130	160	148	132	119
6 12 kgm.	87.5	85	132	161	147	130	117
7 14 kgm.	103	103	126	148	137	125	120
8 14 kgm.	105	107	135	170	160	130	121
9 11 kgm. control	100.5	103	107	106	106	104	102
10 11 kgm.	100	100	160	160	136	118	
11 15 kgm.	104	105.5		171	158	131.5	121
12 15 kgm.	101	104	133	159	142	130	

changes due to handling. Samples of blood were drawn every half hour, over a period of from 2½ to 3 hours.

Control experiments were performed by administering 50 cc. of water, instead of adrenalin. The animals were subjected to the least possible amount of handling. All the controls showed a constant blood sugar level throughout the experiments. Neither the experimental method nor the administration of water gave any rise in the blood sugar.

The accompanying typical curve shows that the first noticeable effect after the oral administration of adrenalin appears after one-half hour and the blood sugar rises considerably by the end of the first hour; it remains above the normal level for more than 2½ hours. Outside of the blood sugar changes, the animals showed no signs of distress nor manifestations of the action of adrenalin. When administered by stomach tube, adrenalin showed no effect on the blood pressure.

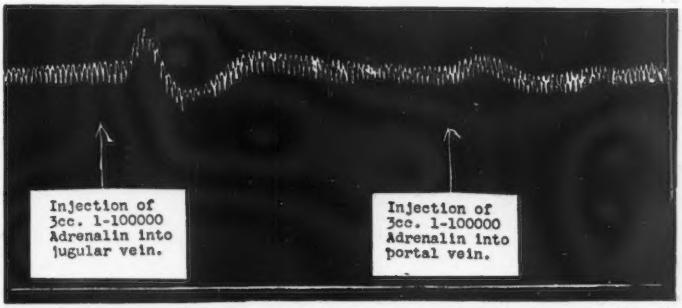


Fig. 2. Injection of 3cc. 1-100,000 Adrenalin into jugular vein followed by a similar injection into portal vein.

2. *Injection of Adrenalin.*

The dogs were anesthetized with ether, using the drop method. As soon as the animals were under, the femoral arteries in both legs were exposed; next the jugular on the left side, and finally the abdomen was opened by means of a median longitudinal incision, sufficiently large to permit access to the portal veins, vena cava, and the liver.

The exposed parts were kept covered with absorbent cotton soaked with warm Locke's solution. The abdomen was covered with towels moistened in Locke's solution, and kept warm by a 200-watt light over the operating table. After the animal was completely prepared, the blood pressure apparatus was connected to one of the femoral arteries.

Adrenalin was injected into the jugular, vena cava, portal vein, and the liver. Care was taken to time each injection with a stop watch in order to insure uniformity. Injections of 3 cc. of 1-100,000 were made first into the jugular and followed by an equivalent injection into the portal, and vice-versa. In order to reduce the volume of the injections, 1 cc. of 1-40,000 were also tried on the same animals.

The accompanying records show that the rise in blood pressure, following injection of 3 cc. of 1-100,000 into the portal vein, was just perceptible. When 1 cc. of 1-40,000 was injected into the portal vein, the rise in blood pressure was slightly more pronounced, but still considerably less than that due to similar injections into the jugular. Injections into the vena cava or the jugular always showed greater effects on the blood pressure than injections into the portal vein, or into the liver. Further work is in progress to determine the exact location of the removal of the pressor action of adrenalin when given orally.

SUMMARY AND CONCLUSIONS

1. Adrenalin was administered by stomach tube to 12 dogs. It caused a rise in the blood sugar level.

2. Adrenalin is absorbed, therefore, through the gastro-enteric tract, other than the mouth and throat.

3. None of the other usually apparent effects of adrenalin were noted.

4. The blood pressure was not affected.

5. Injections of adrenalin into the jugular and the vena cava gave materially greater rises in blood pressure than did equivalent injections into the portal vein or into the liver.

6. Apparently the liver removes most of the pressor effect of adrenalin.

7. It appears that the liver is able to remove the pressor effect of adrenalin as fast as the drug is absorbed, when administered by stomach tube.

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INFRA-RED STERILITY: PRELIMINARY REPORT

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Recent work (1) has shown that sterility can be produced in males by the application of heat to the testes. Snyder (2) ascribes the sterilizing effect of x-rays in rats to the heating effect. Recently Zalewski and Trifonoff (3) have reported that the local application of infra-red rays to the testes may be of benefit in clinical gonad insufficiency. This might be due secondarily to destructive effects on the spermatogenic tissue leading to better nutrition of the interstitial cells.

We have studied the sterilizing effect of infra-red rays in rats using both mating tests and histological study of the glands as criteria of the effects in the testes. Complementary studies have been made using heated air as the sterilizing agent.

Some preliminary experiments were made in March, 1927, two males being treated with infra-red rays. The apparatus for treatment consisted of a wooden box containing an infra-red burner. Directly above this burner a hole 2½ x 1½ inches was cut, which allowed the superimposed testes to be directly exposed to the rays. A fairly constant temperature of 48°C., varying no more than half a degree at the aperture, was obtained by this apparatus. Rats that have been handled frequently do not seem to mind the treatment and they may be held in position by the tail.

After a treatment of five minutes, each male was penned with two females. Each was found to be fertile up to about fifty-four days after treatment, when they became sterile for a period of a month. After this they were again fertile. Vaginal smears taken after copulation during the latter part of the sterile period showed no living spermatozoa present. Sterility produced by this means evidently does not produce senility. The mating instincts are at no time lost. This fact has been previously observed by Young (l. c.) in his work with guinea pigs.

It seemed desirable to determine whether the sterility produced in this experiment was due to some inherent ray in the infra-red or whether the results were traceable to thermal factors. To determine this point another series of experiments was begun in November. Four checked males were treated for five minutes with infra-red rays in the manner previously described. Four other males were similarly treated for five minutes at 48°C., but with air heated by a steam boiler. The males were then mated.

The mating tests, while indicating the existence of sterility, do not very sharply define its beginning or ending unless a rather large number of females having various oestrus cycles are penned with a single male.

Our facilities did not permit the penning of more than two females with a male, hence the indicated periods at which sterility begins and ends are quite variable.

Nevertheless, it was shown that there is a definite sterility period which is in turn followed by a fertility period, as the following data, based upon breeding tests, indicate:

Heated Air Treatment

Rats	Sterility Begins— Days after Treatment	Sterility Ends— Days after Treatment
No. 93	16	41
No. 94	24	53
No. 95	24	61
No. 96	27	82

Infra-Red Treatment

No. 97	Not determined	47
No. 98	38	85
No. 99	34	65
No. 100	Not determined	84

Young checked his sterility work with guinea pigs by histological study. He found that germinal degeneration took place in a rather definite order. "Large primary spermatocytes, secondary spermatocytes, young spermatids, a few spermatogonia are affected first. Subsequently, the older spermatids, spermatozoa within the seminiferous tubules and the early growth stages of the primary spermatocytes are affected." The epididymal sperm seems to be protected but the sperm in the distal and proximal ends undergo degeneration and disappear, apparently by liquifaction.

Snyder does not give a thorough account of his histological studies; however, during the sterility period he failed to observe any active stages of spermatogenesis. Upon his observations he concluded that the roentgen rays affect the actively growing tissue more than quiescent tissue; spermatozoa and young spermatogonia are most resistive.

Studies of degeneration in the testis were made upon two male rats treated for fifteen minutes with heated air and two others treated with infra-red rays for the same length of time. These rats had been previously checked in the usual manner and found to be fertile before treatment. Rat No. 1 (heated air) and No. 3 (infra-red) were castrated unilaterally on the seventh day, the left testis being removed. On the fourteenth day rats No. 2 (heated air) and No. 4 (infra-red) were castrated in the same manner except the right testis was removed. On the twenty-first day rats Nos. 1 and 3 and on the twenty-eighth day Nos. 2 and 4 were killed and the remaining testes taken.

The tissues were killed in Bouin's fluid, imbedded in paraffin and sectioned at 8 microns. They were stained with Gentian violet. The

epididymus and the vas deferens were sectioned also. In order to study the distribution of degenerative changes sections were taken at short distances apart throughout the entire testis. A normal testis prepared in a similar manner was used for comparison.

As nearly as possible the following chart indicates the comparative observations of the tissue.

HEATED AIR SERIES

	7 Days	14 Days	21 Days	28 Days
Sperm in seminiferous tubules.	Many normal sperm, quite a few degenerated to some extent.	As many sperm present as in 7-day, but more degenerated ones and degenerated to a greater degree.	A very few normal sperm. Also a few degenerated ones.	More normal sperm and spermatids. Most tubules regenerated to great extent, some still degenerate.
Sperm in ducts.	Most ducts very full of normal sperm. A few small ducts with none.	Not as many sperm present. No noticeable degeneration.	Still fewer sperm present. Quite a few have degenerated.	Most tubules in same condition as in 21 days. Many degenerate sperm. Some tubes in which all sperm are degenerate.
Nuclear figures.	General degeneration. Half tubules show decided degeneration of chromatin. A few tubules almost empty. Only a nuclear figure here and there.	Slight regeneration, a few more nuclear figures.	Some tubules still badly degenerated; more apparent regeneration with many nuclear figures.	General regeneration with many nuclear figures present. A few tubules still in bad condition.

INFRA-RED SERIES

	7 Days	14 Days	21 Days	28 Days
Sperm in seminiferous tubules.	Many normal sperm, a few degenerated ones.	Numerous sperm still present, but many degenerated ones.	Few normal sperm. Many degenerated heads and tails.	Practically no sperm; some degenerated heads and tails.
Sperm and ducts.	Tubules full of normal sperm.	About as many sperm in ducts, but a few are empty, and some sperms are quite degenerate.	Only one-half as many as in 14-day; a lot of degenerated sperm, several tubules empty.	No normal sperm. Very few chromatin dots in center of few of ducts.
Nuclear figures.	Degenerate chromatin in half of the tubules; general cell condition slightly different from steam heat of same age; few nuclear figures.	Numerous nuclear figures. Regeneration quite evident in most tubules, but some still degenerate.	Many nuclear figures. A few tubules still quite degenerate.	Many more nuclear figures. Activity of cells next to the tubule wall quite evident.

In order to see if it were possible to establish a second sterility period, two males from each set were given a second treatment for the same length of time. This was given thirty-five days after the first treatment. A second sterility period occurs in animals treated in this manner, as is shown by the following table.

Single Hot Air Treatment

Rat	Days after Treatment First Sterility Begins	Ends	Days after Treatment Second Sterility Begins	Ends
No. 96	24	53	75	102
No. 94	27	82	103	145
	Infra-Red Treatment			
No. 98	Undetermined	47	77	Undetermined
No. 97	38	65	92	113

In this experiment the second sterility period seems to be due to the second treatment. However, in the animals treated but once it was observed that a second sterility period occurred which, to all appearances, was similar to that of the animals treated twice.

The following table may be compared with the previous one.

Single Hot Air Treatment

Rat	Days after Treatment First Sterility Begins	Ends	Days after Treatment Second Sterility Begins	Ends
No. 93	16	41	60	97
No. 95	24	61	80	102
	Infra-Red Treatment			
No. 99	34	65	86	
No. 100		84	109	

It is quite evident that there is a general similarity in the effects produced by infra-red and heated air. However, since there are so many individual differences which play a great part, many more animals should be used; in fact, we are continuing the work at present with considerably larger numbers.

(Since the above was written 37 additional animals have been treated, all but one of which have become sterile.)

SUMMARY.

Since sterility can be produced by hot air and infra-red rays, it seems reasonable to conclude that the causal factor in the infra-red is thermal.

This work confirms the work of Young, Snyder and several others, and adds a new agent for sterilization—one that can be administered with the minimum inconvenience and danger.

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2. Snyder, L. H.: The effect of x-rays on the fertility of rats. Am. Naturalist, **59**: 87-91. 1925.
3. Zalewski, M. and Mme. Trifonoff: Les rayons ultraviolets et infra-rouges et les glandes à sécrétion interne. Progrès méd. **42**: 1773-1777. 1927.

Abstract Department

Malignant tumors of the adrenal in children with report of a case. Bendixen, P. A. and F. H. Lamb, J. Lab. & Clin. Med. **12**: 132. 1926.

A brief review of the literature on the subject with report of a case occurring in a girl, 5 years old. Suprarenal medullary malignancy is not an altogether unusual occurrence. In the majority of cases an orbital hemorrhage is the first sign observed, and it may occur before any tumor is palpable. The orbit first involved is often on the same side as the primary tumor, although the case reported was an exception. Diagnosis should not be difficult, once the orbital hemorrhage has occurred. The disease is likely to be mistaken for trauma, chloroma and scurvy. Surgical interference can be of no avail except as a palliative to drain a pyonephrosis or to meet other complications, as the metastases occur usually before a diagnosis can be made. Metastases probably occur through the lymph stream. The malignancy rarely metastasizes to the skin. The medulla of the suprarenal gland being neuroectodermic in origin, these malignant tumors are similar in their histological structure to malignant neoplasms of the sympathetic nervous system, and they are correctly designated as neuroblastoma.—I. B.

Hemorrhage of the suprarenals in the new born infant. Goldzieher, M. A. and H. M. Greenwald, Am. J. Dis. Child. **36**: 324. 1928.

Suprarenal hemorrhage in the new born infant can be diagnosed from its symptoms, such as sudden onset of temperature and rapid breathing and occasionally by the presence of a palpable tumor in the abdomen or by punctiform hemorrhages of the skin or mucous membranes. Exsanguination or intestinal obstruction may justify surgical intervention, otherwise, patients with the symptoms of acute cortical insufficiency should be treated by the continued administration of the cortical hormone. Two cases are reported in which adrenal hemorrhage was diagnosed; one came to autopsy and the other recovered.—M. B. G.

Experiments on the function of the interrenal organs of selachians (Untersuchungen über die Funktion des Interrenalorgans der Selachier). Kisch, B., Arch. f. d. ges. Physiol, **219**: 426. 1928.

Complete removal of the interrenal gland from selachians leads rapidly to death. Sham-operated animals lived three or four times as long. The gland in *Torpedo ocellata* is two or three times as great as that in *T. marmorata* of the same weight. The latter survive the operation two or three times as long. Following the extirpation a persistent balling of the pigment of the skin chromatophores, whereby the animals take on a dirty-gray color, slowing of breathing, muscle weakness, shortening of the body musculature, hypersensitivity to oxygen scarcity, and early death, which often suddenly follows intensive muscular activity, occurs. Hence the symptoms of adynamia, respiratory disturbance, increased sensitivity to oxygen failure and sudden death after intense muscular activity, which follow adrenalectomy in mammals, must be attributed to removal of the adrenal cortex. It is considered that the interrenal tissue (the adrenal cortex in mammals) gives to the circulation some compound which favors the oxidative decomposition of definite metabolic products, which in excess have a toxic action leading to the above mentioned symptoms and finally to death. Anything increasing the concentration of these products, such as muscular activity, lowering of oxygen concentration, loss of blood, must increase the symptoms and accelerate death. Injection of acid extracts of interrenal tissue may delay the symptoms in selachians for hours. Injections of sea-water, adrenine, or liver extract, have no such effect.—A. T. C.

The amount of adrenin in the adrenal glands in total starvation (Sur la teneur en adrenaline des capsule surrenales dans l'inanition totale). Mouriquand, G. and A. Leulier, Compt. rend. Soc. de biol. **99**: 280. 1928.

In guinea pigs kept five days without food, but given water, the adrenals showed an increase in both the free and total adrenin.—J. C. D.

The effect of subcutaneously injected epinephrin in normal human subjects. Koppanyi, T., Proc. Soc. Exper. Biol. & Med. **25**: 744. 1928.

Six young, healthy medical students were subjected to subcutaneous epinephrin injections (0.4 cc. of a 1:1000 solution). Before injection the normal systolic and diastolic blood pressure and the heart and respiratory rates were determined. From 10 to 15 minutes following the injection of epinephrin there was a rise in blood pressure of 30 to 50 mm. of Hg., a slight increase in the heart and respiratory rates without any massage. The injected area was blanched, the face pale, there was a slight muscular twitching in the arms and legs, and a thumping, palpitating heart was evident. The subjects felt slight headache, throbbing in the head, some nausea, the mouth was dry, and there was in some cases subjective sensation of warmth; in others, the hands and feet felt cold. Nervousness and general feeling of anxiety were evident in most subjects, whereas one subject appeared to be in a fighting mood. The injected areas were massaged from 15 minutes to 48 hours following injections. In the course of the 48 hours, the area was massaged about 25 times. On the whole, all symptoms which appeared following epinephrin injection without massage, could be duplicated by massaging the injected area, for about 48 hours. They were, however, much less marked, the blood pressure rises, for instance, being seldom more than from 7 to 15 mm. of Hg. The rise was practically the same when one massaged the area 20 minutes or 20 hours following the injection. One subject developed constipation following the injection.—Author's Abst. (abbreviated).

Suprarenal apoplexy, bilateral. Pearl, F. V. and H. Brunn, Surg. Gynec. Obst. **47**: 393. 1928.

A case of bilateral suprarenal apoplexy of the adrenals in a man aged 45 years is described. The literature is reviewed. At postmortem this case showed almost complete destruction of adrenal tissue.—A. T. C.

The influence of the adrenals on the urea-formation and barrier-function of the liver (Ueber den Einfluss der Nebennieren auf die harnstoffbildende und Barrierefunktion der Leber). Putschkow, N. W. and W. W. Krassnow, Arch. f. d. ges. Physiol. **220**: 44. 1928.

Amino-acid and amino nitrogen increases in the blood and urine following adrenal extirpation, while at the same time there is a sudden decrease in urea content. These findings indicate cessation of liver function and correspond to those following liver extirpation. The isolated liver of adrenalectomized animals acts on ammonium salts and biogenous amines more feebly than the normal liver. Extract of adrenals restores the barrier function of the liver to normal. The active principle of the adrenals is extraordinarily labile and decomposes in 15 to 20 minutes. It is not adrenin and is absent from other body organs.—A. T. C.

A study of the pigment in Addison's disease. Spohr, C. and R. A. Moore, J. Lab. & Clin. Med. **12**: 438. 1927.

The ultimate chemical analysis of a pigment derived from the lymph glands in a case of Addison's disease is reported. The evidence seems to point that this pigment is a melanin and the absence of any other explainable cause of the melaninosis than the Addison's disease would lead one to believe that there was more than a casual relationship between the two. The authors believe the pigment laid down in the tissues to be melanin, and that it bears a direct relationship to the condition responsible for the pathologic complex of Addison's disease.—I. B.

New clinical and experimental studies of the inter-relations of the thyroid, adrenals and the nervous system. Crile, G. W., New England J. Med. **198**: 988. 1928.

The crises of hyperthyroidism are due to the interaction of the thyroid and adrenal medulla. Thyroid extract after a latent period increases the electric conductivity and capacity of the organs and tissues in the body. Adrenin has an immediate effect. It raises the conductivity, temperature, and capacity of nervous tissue and the adrenal medulla, while it has the opposite effect on the other tissues. This, it would seem, increases the difference in potential between

the different tissues. "It would appear from the finding (the increased conductivity and capacity of the medulla after adrenin injections) that the medulla of the adrenal functions as nerve tissue; perhaps it is the brain of the vegetative system, its probable function being to charge up—to energize the vegetative system." On this theory, four cases of hyperthyroidism were treated by a hemi-adrenalectomy with very encouraging results.—J. C. D.

Action of ephedrin on intestine and bronchi. Halsey, J. T., Proc. Soc. Exper. Biol. & Med. **26**; 16. 1928.

In more than 100 experiments, no evidence of a depressant action of ephedrin on the isolated rabbit intestine was found.—M. O. L.

Experimental histology and clinical observations on the destruction by chemical means of the sympathetic of the spermatic cord (Observaciones experimentales histológicas y clínicas sobre la simpatectomía química del cordón espermática. Cassuto, A., Rev. Sud-Am. de endocrinol. **11**: 221. 1928. Abst., Physiol. Absts. **13**: 319.

It is claimed that painting the internal spermatic artery to the vas deferens with a 5 per cent solution of phenol destroys the sympathetic nerves to these vessels, thereby causing increased blood flow to the testicles. This is followed in men and dogs by increased spermatogenesis and return of sexual potency.

Ripe follicles are not essential for the appearance of the oestrous (La présence du follicule mur n'est pas indispensable a l'apparation de l'oestrous). Courrier, R., Compt. rend. Soc. de biol. **99**: 26. 1928.

In the bat, the early stages of oestrous appear normally in the absence of ripe follicles.—J. C. D.

Does the follicular hormone inhibit that of the corpus luteum? (L'hormone folliculaire inhibe-t-elle l'hormone lutéinique?). Courrier, R., Compt. rend. Soc. de biol. **99**: 224. 1928.

Rabbits, five days after mating, were injected with follicular hormone, twice daily for six days. On autopsy, there were no corpora lutea, no pregnancies and the endometrium was of the normal type.—J. C. D.

Relations between the hormone of the corpus luteum and of the follicle (Les rapports qui existent entre les hormones folliculaire et luteinique).
Follicular hormone cannot replace that of the corpus luteum (La folliculine ne peut suppleer l'hormone luteinique). Courrier, R. and M. Masse, Compt. rend. Soc. de biol. **99**: 263; 265. 1928.

Five days after mating, rabbits were spayed and then given regular injections of follicular hormone in varied doses. Under these conditions, implantation does not take place. Histological study of the uterus shows that while folliculin can maintain the uterine mucosa in an advanced state of preparation for implantation, it cannot cause the final changes, which take place when the corpus luteum is present. Folliculine does, however, have a marked action in developing the uterine smooth muscle. These experiments support the theory of the double nature of the ovarian hormones.—J. C. D.

The female sex hormone, clinical experiences with various ovarian preparations. (No title given in the original German report.) Fraenkel, L., Therap. d. Gegenw. **68**: 524. 1927.

The female sex hormone is found in the ovarian follicle, corpus luteum, decidua, placenta, blood and milk, but not in the cerebro-spinal fluid. With extracts made from corpora lutea the writer was able to allay deficiency disturbances, but did not succeed in stimulating menstruation. The preparations were effective when given by mouth, but the dosage had to be 20 times the subcutaneous dose because of partial destruction in the gastro-intestinal tract. The writer is very skeptical about the corpus luteum containing a stimulating substance (Agomensin) and an inhibiting substance (Sistomensin). The author treated 114 subjects who had been carefully selected because of the following indications: amenorrhea, splasia of the uterus and genitalia; infantilism, secondary atrophy following surgical or x-ray castration, and endocrine disturb-

ances in which amenorrhea is an important symptom, notably myxedema and dystrophia adiposo-genitalis. The ovarian extracts used in treating this series of cases were Menformon, Biedl's Hormovar, and an American preparation. Evidences of the effectiveness of treatment were the following: Enlargement of the breasts, cramps in the loins, premenstrual changes in the uterus and vagina, and growth of secondary sex characteristics. Of the 114 treated subjects, 20 were excluded for various reasons, and of the remaining cases, 30.5 per cent showed a positive result, 9.5 per cent were inconclusive, and 60 per cent were negative. Many authors have reported similar results, and only Zondek and Joseph have reported more favorable results. The treatment is not much better than ovarian transplantation.—E. P. Bugbee.

Experiments on rat oestrus and the influence on it of ovarian extract and bile (Untersuchungen über den Rattenoestrus und seine Beeinflussung durch Ovarialextrakte und Galle). Gsell-Busse, M. A., Arch. f. d. ges. Physiol. **219**: 626. 1928.

The ovarian hormone is both water- and lipoid-soluble, but has a great affinity to lipoids. Commercial sodium taurocholate contains an active principle which resembles the ovarian hormone in its action.—A. T. C.

Sterilization by ovarian hormones (Die hormoale sterilisierung des Weiblichen Tierkorpers). Haberlandt, L., Wien. klin. Wchnschr. **41**: 553. 1928.

Haberlandt was able to produce a temporary sterility in a number of species of rodents by transplanting into sexually mature females ovaries from pregnant animals; by daily subcutaneous injection over a number of weeks of ovarian and corpus luteum extract from pregnant animals and by feeding the ovarian and corpus luteum extracts and also placenta extracts daily over a period of weeks. He points out the therapeutic possibilities of these findings in human females.—M. Smeltzer.

Studies on the oestrus cycle in the rat. IV. The basal metabolism during the oestrus cycle. Lee, M. O., Am. J. Phyiol. **86**: 694. 1928.

A total of 282 basal metabolic rate determinations was made on nine female rats during all stages of the oestrus cycle. In all of the animals an increased basal heat production was observed in the last 10 hours of stage V (dioestrum) and in the first 6 hours of stage I (pro-oestrum). The amount of this increase above the level characteristic of the remainder of the cycle varied from 5 to 20 per cent, with an average of 13 per cent. Although this increase is not great, the analysis of the data indicates that it is statistically valid. No change in the basal metabolic level was found in any other phase of the cycle. Even during stage II (oestrus), which is characterized by a marked increase in voluntary activity, the average basal heat production showed no change. The increased heat production towards the end of the dioestrum is comparable to a slight increase reported in women at menstruation. Respiratory quotient determinations were made in two rats during all stages of the cycle. No consistent changes were found.—Author's Abst.

The question of the sex-specificity of the internal secretions of the gonads. Action of the secretion and alterations of the pituitary of castrated rats (Zur Frage der Geschlechtsspezifität der Keimdrüseninkrete. Inkretwirkung und Veränderung der Kastrationshypophyse der Batte). Lehmann, J., Arch. f. d. ges. Physiol. **216**: 729. 1927.

The pituitary of castrated rats shows a relative increase of basophil and eosinophil epithelium above that of normal animals. Implantation of human testicular tissue or injections of aqueous extracts from it restores this ratio to normal, indicating that the gonadal internal secretion is not specific to species. Male animals only react to testicular and female to ovarian preparations, whence sex-specificity is deduced.—A. T. C.

Transplantation of preserved ovary. I. Endocrine action of ovaries preserved on ice (Transplantation von konservierten Ovarium. I. Endokrine Wirkung von auf Eis konservierten Ovarien). Lipschütz, A., Arch. f .d. ges. Physiol. **220**: 11. 1928.

Guinea-pig ovaries kept at temperatures below 0° C. are so damaged that they produce no endocrine action following transplantation, but merely degen-

erate. On the other hand, ovaries kept for 1 to 16 days at + 1 to + 3° are still endocrinally active following transplantation, as shown by production of typical feminization of male guinea-pigs, with mammary development leading to lactation. Nevertheless, some damage results from such preservation; the proportion of positive results is less than with transplants of fresh ovaries, the latent period is longer, and the transplant survives a shorter time.—A. T. C.

Transplantation of preserved ovary. II. Endocrine action of ovaries preserved at room temperature (Transplantation von konservierten Ovarium. II. Endokrine Wirkung von bei Zimmertemperatur konservierten Ovarien). Lipschütz, A., Arch. f. d. ges. Physiol. **220**: 29. 1928.

Ovaries kept at 14-20° C. can produce endocrine action after transplantation, but the amount of damage to them seems greater than to those preserved on ice.—A. T. C.

Transplantation of preserved ovary. III. The microscopic condition of isolated and transplanted ovaries (Transplantation von konservierten Ovarium. III. Das microscopische Verhalten des isolierten und transplantierten Ovariums). Lipschütz, A., Arch. f. d. ges. Physiol. **220**: 321. 1928.

A comparison between normal and isolated ovaries from the same animal shows that following isolation without nutriment marked damage to the primary follicles ensues, whereby a number of them die. This explains the smaller percentage of positive results obtained when preserved instead of fresh ovarian transplants are used.—A. T. C.

Activity studies on castrated male and female rats with testicular grafts, in correlation with histological studies of the grafts. Richter, C. P. and G. B. Wislocki, Am. J. Physiol. **86**: 651. 1928.

Testes were implanted into 36 animals, 17 males and 19 females. Six of the males and 2 of the females listed as "functional takes" showed a definite increase in activity; one male and one female listed as "possible functional takes" showed a doubtful increase; and all of the remaining animals listed as "functional non-takes" showed no change at all in the activity level. Large grafts were found in all of the animals showing a definite increase in activity, with the exception of one female which probably had not been fully spayed. Small grafts were found in the 2 "possible takes" and in 8 of the 11 male "non-takes" and 4 of the 16 female "non-takes." Microscopic study revealed that the testicular grafts were not absolutely normal in any of the animals. In general, however, it appeared that the increase in activity stands in direct proportion to the state of preservation of the graft, and that the most important part of the testes for the production of the activity increase is the interstitial tissue. The increase in activity produced by transplanted testes was much less than that produced by transplanted ovaries.—R. G. H.

Reactivation of the senile ovary and of the female organism by hormonal methods (Reaktivierung des senilen Ovars und des weiblichen Gesamtorganismus auf hormonalem Wege). Steinach, E., H. Kun and W. Hohlweg, Arch. f. d. ges. Physiol. **219**: 325. 1928.

Use of an aqueous ovarian preparation gave precisely similar results to those following ovarian transplantation into senile female rats—recommencement of oestrus, regeneration of ovaries and uterus, and reactivation of the whole organism.—A. T. C.

Preparation of the female sex hormone from the urine, especially from the urine of pregnant women (Darstellung des Weiblichen Sexualhormons aus dem Harn, inbesondere dem Harn von Schwangeren). Zondek, B., Klin. Wchnschr. **7**: 485. 1928.

The female sex hormone forms a true aqueous solution and can be dialyzed readily. It is present in large quantities in the urine of pregnant women and pregnant animals. In certain conditions other than pregnancy, as for example the menopause, the urine contains large quantities of the hormone. A liter of urine from a woman in the last month of pregnancy yields 4000 to 6000 Mouse Units, and occasionally even as much as 10,000 Mouse Units. This is twice as much activity as can be obtained from a liter of ovarian follicular fluid from

cows. If one reckons that 1 unit is represented by 0.001 mgm. of solids then 1 gram of the hormone can be obtained from 200 liters of urine. The female sex hormone dialyzes readily through various kinds of membranes. It dialyzes more quickly than many other constituents of the urine. The preparation of the hormone from urine is easier than from placenta or follicular fluid which has a high protein content. The method of preparation may be the same but a slight modification is desirable. (1) The filtered urine is extracted with some lipoid solvent, other than alcohol, to eliminate urea. (2) The extract is treated with hot alkali, taken up in water and shaken with ether. (3) The ether soluble part is taken up in distilled water or weak acetic acid heated and filtered. The hormone is contained in the filtrate which is water-clear, bright and free from color and odor. The total solids are only 0.01 to 0.001 mgm. per Mouse Unit.—E. P. Bugbee.

The heart hormone (Ueber das Herzhormon). Rigler, R. and R. Singer, Arch. f. d. ges. Physiol. **220**: 56. 1928.

The specificity of Haberlandt's "hormone" is denied. It is not a hormone in the strict sense of the word.—A. T. C.

Hypodynamic heart condition and the "heart hormone" (Hypodynamischer Herzzustand und "Herzhormon"). Teitel-Bernard, A., Arch. f. d. ges. Physiol. **220**: 212. 1928.

The activity of hypodynamic hearts can be increased by forcing in air or by other mechanical means of enlargement, whereby active substances are pressed out of the heart musculature. These are not identical with Loewi's accelerating substance, and are not hormones.—A. T. C.

Is there an antagonism between the water soluble extract of anterior lobe and folliculine? (Existe-t-il un antagonisme entre l'extrait hydrosoluble du lobe antérieur de l'hypophyse et la folliculine?) Brouha, L., Compt. rend. soc. de biol. **99**: 43. 1928.

If rats are injected simultaneously with both these substances, the usual effects of folliculine are evident: the precocious sexual development and normal oestrous cycle. The pituitary extract acts, therefore, through its rapid alteration of the corpora lutea with the resulting suppression of the follicular hormone and not by direct antagonism to it.—J. C. D.

The action on diabetes insipidus of powdered posterior lobe of hypophysis (Action de la poudre de lobe postérieur d'hypophyse sur le diabète insipede). Choay, A. and L. Choay, Compt. rend. Soc. de biol. **99**: 359. 1928.

Powder from beef glands dried in the cold in vacuo is snuffed up into the nose like snuff. Four doses per day, of from 20 to 50 mgm. each, were used in an adult passing 15 liters of urine. His output fell to 3 liters. Where the output is over 20 liters, this method can be used only to supplement the usual injections of hypophysis. In 12 less severe cases it has proved successful over a period of five years.—J. C. D.

The various morphological alterations of the rhinopharynx in relation to the hypophyseal syndrome (De quelques altérations morphologiques rhinopharyngèes en relation avec le syndrome hypophysaire). Curchod, E., Schweiz. med. Wchnschr. **58**: 537. 1928.

The author emphasizes the fact that the epithelial portion of the pituitary is developed from the ectodermal pharyngeal pouch. For this reason the pituitary is related to the morphological development of the nose and nasal appendages. He describes a case of acromegaly in a woman 21 years of age, weight 65 kgm., height 65 inches. The nose was very broad throughout the transverse diameter. The turbinates were very large and there was a difusse edematous infiltration of the nasal mucous membrane. The inferior turbinate was so large that it produced a complete obstruction of the anterior nares. Anatomical pathological examination revealed an angiomatous hyperplasia of the mucous membrane. The posterior pharynx had areas of hyperplastic lymphoid tissue. The lingual tonsils were very large. The pharyngeal tonsils were rather small, as they had been partially excised. X-ray of the skull showed a voluminous frontal sinus, the sella turcica was large but within normal limits. Thymus findings were negative. The muscular development

was good and the basal metabolism was 45% above normal. The anterior lobe of the pituitary influences the development and form of the nose as well as of the nasal appendages.—R. C. Moehlig.

The mechanism of the influencing of blood sugar by pituitary extracts (Beiträge zum Mechanismus der Blutzuckerbeeinflussung durch Hypophysenextrakte). Fritz, G., Arch. f. d. ges. Physiol. **220**: 101. 1928.

Intramuscular injection of posterior pituitary extract causes increase of blood sugar in mammals. The action is secondary through mobilization of adrenin: it is not produced in adrenalectomized animals. The mobilization of adrenin results from general sympathetic stimulation.—A. T. C.

Pituitary extract in pyelitis. Miller, J. A., New York State J. Med. **28**: 720. 1928.

The report is based upon the administration of pituitary extract in parturient and in non-pregnant women. In cases where pituitary extract was used pyelitis did not occur as a post partum complication. Where pyelitis occurred before delivery, the use of pituitary extract in inducing labor as a routine measure effected an immediate cure. The injection of pituitary extract, 1 cc. at intervals of 5 days for 3 injections, prevented the recurrence of pyelitis in chronic cases of non-pregnant pyelitis. Whether this cure is permanent or not remains to be seen. Pituitary extract has the effect of restoring the tonus of the ureter, increasing the contractility and preventing stasis of urine and resultant infection of the genito-urinary tract.—M. B. G.

Histological evidence of colloid absorption directly by the blood-vessels of pars anterior of the human hypophysis. Rasmussen, A. T., Quart. J. Exper. Physiol. **17**: 149. 1927.

Histological examination of about a hundred apparently normal adult human hypophyses from cases of accidental death revealed colloid in the blood-vessels of only two specimens. In one of these, a young pregnant woman, it was abundant and could be seen in both the capsular veins of the anterior lobe, veins emerging from the region of the stalk, as well as in the sinusoids proper. The method by which the colloid globules get into the vascular channels is not evident. There are indications of degeneration in some of the cells surrounding the colloid in many of the small vescicles or pseudoacini in pars anterior, and the colloid may be separated from the interstitial tissue and blood channels by only very thin flattened cells, but conditions where the colloid is actually in the process of entering the sinusoids were not located even after diligent search in supposedly very favorable material.—Author's Summary.

The weight of the principal components of the normal male adult human hypophysis cerebri. Rasmussen, A. T., Am. J. Anat. **42**: 1. 1928.

An attempt was made to supply more accurate data, including the more useful statistical constants, on the size of the main body of the hypophysis and its constituent parts, by applying the paper-weight method to serial sections of 111 selected normal male adult human hypophyses, twenty to twenty-six years of age, from cases of sudden and usually accidental death. The method used gives the fresh weight of the gland after dissecting of as much of the adherent connective tissue as possible and removing the stalk, which accounts for a somewhat lower average weight than is usually given for the organ as a whole. The average weight of the main body of the hypophysis, including a variable amount of connective tissue or capsule, is 570 mgm. The extreme values are 400 mgm. and 855 mgm. The frequency distribution of the weights is, in general, of the common fairly symmetrical unimodal type, except in the case of the colloid and parenchyma of pars intermedia, where it is greatly skewed in the positive direction. The variability, as expressed by the coefficient of variation, is highest in the case of pars intermedia (being around 90 or over, depending on whether or not the colloid is included); less in the posterior lobe (29); still less in the anterior lobe (21); and least in the gland as a whole (18). The anterior lobe decreases noticeably after fifty years of age. The coefficient of correlation (r) between age and weight of the anterior lobe is —.293+.059. The posterior lobe probably tends to increase slightly with age. As a result, there is a less marked decrease in the weight of the whole gland than in the anterior lobe. The parenchyma of pars intermedia

seems to increase distinctly with age, but when tested statistically the results are not significant, on account of the limited number of cases and the great individual variability. There is no evidence the colloid increases with age in the adult.—Author's Summary (Abbreviated).

The hypophysis and the urinary excretion of inorganic phosphate, sulphate and chloride. Tung, P. C., H. C. Chang and S. M. Ling, Chinese J. Physiol. **2**: 231. 1928.

This investigation was made to test the validity of the claim that the excretion of urinary phosphate is readily abolished by the extirpation of the pituitary body or injury to the tuber cinereum, even though the phosphate content of the serum is not materially changed. Six dogs survived hypophysectomy from 1 to 16 days, and the excretion of phosphate was found to continue uninterruptedly. In five acute experiments a typical fall of urinary chlorides occurred after the operation. The phosphate output, however, first rose and then fell up to the fourth or fifth hour, after which a recovery phase appeared. This temporary disturbance of inorganic phosphate excretion was duplicated in two control experiments by the application of fresh pituitary extract to the brain surface. It is concluded that the suggestion that removal of hypophyseal control abolishes the kidney excretion of inorganic phosphate is open to serious question.—L. G. Kilborn.

The function of the pancreas in tadpoles (Le fonctionnement du pancréas chez les larves d'Amphibiens). Functional correlation between the thyroid and internal secretion of pancreas in tadpoles (Corrélation fonctionnelle le glande thyroïde et le pancréas endocrine chez les larves d'Amphibiens). Aron, M., Compt. rend. Soc. de biol. **99**: 213; 215. 1928.

Glycogen appears in the liver of tadpoles just before metamorphosis. The pancreas is essential for this appearance of sugar but not for metamorphosis. Feeding thyroid just before metamorphosis increases the glycogen in the liver. —J. C. D.

The effect of hypodermic insulin on the fasting blood sugar in normal and diabetic subjects in relation to percentage normal weight. Bartlett, W. M., J. Lab. & Clin. Med. **12**: 115. 1926.

Blood sugar curves following hypodermic administration of insulin are reported in 37 subjects. Underweight normal subjects and underweight diabetic subjects were found most sensitive to the blood sugar lowering effect of insulin. Obese normal subjects are the least sensitive to insulin. The effect of insulin occurs most slowly in obese diabetics and normal subjects of normal weight. The blood sugar curve following insulin is not specific enough in the diabetic patient to be used as a diagnostic test.—I. B.

A contribution to the nature of diabetes. A mathematical derivation of the blood glucose curve. Ervin, D. M., J. Lab. & Clin. Med. **12**: 318. 1927.

By investigating mathematically the condition of diabetes from the blood glucose curve, no evidence of the failure to burn glucose can be obtained. The curve depends upon a decreased rate of glycogen formation.—I. B.

The stimulation of the external and internal secretion of the pancreas by the same excitant after adrenalectomy (Excitation des sécrètions externe et interne du pancréas par le même excitant après surrénalectomie). Gley, E. and R. Hazard, Compt. rend. Soc. de biol. **99**: 195. 1928.

In dogs hydrochloric acid intraduodenally produces a secretion of insulin as well as of pancreatic juice. The action of the insulin on the blood sugar is more marked in adrenalectomized animals, because there is lacking the active secretion of adrenin, which normally accompanies and antagonizes a secretion of insulin.—J. C. D.

Studies on inhibition of insulin activity. Karelitz, S., P. Cohen and S. D. Leader, Proc. Soc. Exper. Biol. & Med. **26**: 11. 1928.

When insulin is mixed with human blood plasma, unwashed blood cells, or pus from suppurated processes, its action is somewhat destroyed. Determinations of the activity of the insulin were made upon rabbits. Plasma from a diabetic and cells from a person with myeloid leukemia caused marked inhibi-

tion of insulin activity. In rabbits injected with typhoid or staphylococcus vaccine, about one half showed a decreased insulin effect 3 hours after vaccine treatment. It is suggested that there is something in human blood plasma which is more abundant in blood cells, more in diabetic blood than in normal blood, and still more in leukemic cells and pus which inhibits or destroys the action of insulin. It is probably more abundant in blood of patients with fever, leucocytosis, suppurative processes, or serum sickness, than in normal state. The extent of inhibition is variable for individuals, but quantitatively proportional to the amount of blood used. The inhibitory substance may be a proteolytic enzyme, because the inhibition is greater with blood cells than with plasma, greater with leukemic cells and pus than with normal blood cells, and because it seems to be stronger during fever or infection or after vaccine injection. Even more significant, with regard to the enzyme-like action, is the experiment in which the plasma or pus heated at 57° for 1 to 2 hours no longer inhibited insulin action.—M. O. L.

Toxicosis of pregnancy treated with insulin [Fünf und vierzig Fälle von Schwangerschaftstoxikosen (Azidosen) mit Insulin behandelt]. Loeser, A., Zentralbl. f. Gynä. **52:** 1405. 1928.

A report on 36 patients with vomiting of pregnancy, 2 with eclampsismus, 3 eclamptic and 4 with pregnancy dermatoses. The treatment lasted anywhere from 10 days to 6 or more weeks. Sugar was added either by rectal drip or else intravenously. The author advises the use of 5 units of insulin subcutaneously 15-30 minutes after sugar has been given. He considers that a unit of insulin takes care of 3-5 gm. of sugar. The dosage of insulin used was as high as 40 units per day in two doses. As soon as feasible the sugar is given by mouth. The average length of time of this treatment is three weeks. In eclampsismus or eclampsia one can begin with 20-40 units of insulin using 1-2 gm. glucose per unit. In the most severe cases of hyperemesis, with a marked tissue dessication and a decreased water content of the liver, glucose in weak concentration is given intravenously in order to supply liquids.
—H. J. J.

Insulin hypersensitiveness: immunologic considerations and case reports. Tuft, L., Am. J. M. Sc. **176:** 707. 1928.

Since 1924 only two cases of urticarial reaction to insulin have been reported. The two additional cases reported in this paper were studied immunologically. The first patient was sensitive to several commercial preparations and also to Abel's recrystallized insulin. Beef and pork pancreas gave similar reactions. The second patient was sensitive to commercial insulin but not to the purified preparation of Abel. Both of these patients had a generalized urticaria and edema. Antibodies to insulin protein were demonstrated in the patients' serum. The author believes that insulin proteins derived from various species of animals are immunologically similar.—E. L.

Some observations on the effect of blueberry leaf extract in diabetes mellitus. Watson, E. M., Canad. M. A. J. **19:** 166. 1928.

Blueberry leaf extract appears to exert a beneficial effect in certain cases of diabetes. Its action is not consistent. Its utility is most apparent in middle-aged or elderly patients and in mild cases. It is of no avail in the emergencies and complications of the disease. It may become an adjunct to insulin. These results are based on 16 cases.—A. T. C.

The use of posters as a method of instruction in a diabetic clinic. Williams, J. R. and M. Vye., J. Lab. & Clin. Med. **14:** 57. 1928.

This paper deals with personal instruction to diabetic patients. The authors insist that instructing the patient relative to pitfalls of diet and other matters of daily life, is the basis upon which the success of all other elements in treatment depends. On admission to the clinic the patient is given a loose leaf book consisting of mimeographed instructions. He is taught the principles of food chemistry, metabolism, diabetes and insulin action. Informal talks in the class room and demonstrations in the kitchen and laboratory are given. This is supplemented by the use of more than 100 posters, each containing a striking picture to emphasize the lessons. Some posters indicate the foods that are safe and useful; others show foods which are dangerous and forbidden.

Also posters concerning exercise, tobacco, music, marriage, personal hygiene, the care of the feet, and so on, are employed.—I. B.

Note on the cause of the increased output of insulin following intravenous injection of non-hypotonic solution of secretin (Sur les causes de l'hyperinsulinemie consecutive a l'injection intraveineuse de solution de secretine non hypotensive). Zunz, E. and J. LaBarre, Compt. rend. Soc. de biol. **99:** 335. 1928.

Double subcardiac section of the vagus in dogs does not abolish the increased output of insulin.

The presence of intra-thymic parathyroid islets and parathyroid-thymic masses in infants (Ilots parathyroïdiens intra-thymiques et glandule parathyroïdo-thymique chez le nourrisson). Duperie, R., Comptes. rend. Soc. de biol. **99:** 324. 1928.

Four cases, from a premature foetus to a nineteen-month infant in which these anomalies occurred, are described.—J. C. D.

The influence of parathormone on bone regeneration. Fine, J. and S. Brown, New England J. Med. **198:** 932. 1928.

In carefully controlled experiments on young dogs, parathyroid extract (Collip's) definitely retarded the regeneration of resected ribs. In older animals the results were not so conclusive but no benefit from the extract could be observed.—J. C. D.

Parathyroid extract-Collip as a diuretic. Reitzel, R. J. and C. T. Stone, J. A. M. A. **91:** 1238. 1928.

The successful use of parathyroid extract-Collip as a diuretic is reported in the case of a woman with odema and ascites, whose reactions to various other drugs were unsatisfactory.—R. G. H.

Parathyroid extract and glucose tolerance in diabetes mellitus. Wishnofsky, M. and J. M. Frankel, J. Lab. & Clin. Med. **14:** 34. 1928.

The glucose tolerance test may be considered an index of the amount of insulin secreted. If parathyroid extract increases the potency of insulin, this should make itself evident in a reduction in the height and length of the blood sugar curve and in the amount of glycosuria. The authors did not find this to be the case. Their results are completely at variance with those of Cammidge and Howard and others. If we are to assume that parathyroid extract-Collip constitutes the sole active principle of the parathyroids, then we are forced to conclude that the latter are not concerned with carbohydrate metabolism.—I. B.

Studies on the action of thyroxine on the animal organism and especially on the heat regulation of warm blood animals (Studien über die Wirkung des Thyroxins auf den tierischen Organismus und insbesondere auf die Wärmeregulation des Gleichwarmblüters). Abderhalden, E. and E. Wertheimer, Arch. f. d. ges. Physiol. **219:** 588. 1928.

Repeated injections of thyroxine into dogs, rabbits and guinea-pigs lead invariably to rapid loss of weight, and, if continued, to death; rats and mice are much moré resistant. Glycogen, especially liver glycogen, is diminished in all animals, even on a rich diet. When di-iodotyrosine, thyroxine, and thyroid are administered in dosage based on iodine content, the first has a very much slighter action. Extremely slight amounts of thyroxine react on the whole organism of tadpoles and the water-form of axolotl, but frogs and the land-form of axolotl are scarcely affected. While di-iodotyrosine shows an enhancing effect on the action of adrenine on heart muscle, thyroxine inhibits this action. Thyroxine, in concentration of 1 in 6000 to 1 in 10000 diminishes the extent of contraction of the heart without affecting its frequency. Rats treated with thyroxine are more susceptible to an increase of external temperature than are normal animals. The latter can maintain their body-temperature within narrower limits. Mice that have been treated with thyroxine do not become pregnant over a considerable interval.—A. T. C.

The pre-operative treatment of Graves' disease by a combination of iodized fatty acid and vitamins A and D. Adamson, G. L. and A. T. Cameron, Canad M. A. J. **19**: 420. 1928.

"Vitiodum," a combination of vitamins A and D and iodo-jecoleic acid, is as effective as Lugol's solution when administered in Graves' disease. Its beneficial action, and the limits of that action, closely resemble those of Lugol's solution. It did not, in the series of cases examined, produce any gastro-intestinal disturbance during or following its action. The results suggest that neither the vitamins nor the iodo-fatty acid alone are effective. They suggest also the desirability of investigating as widely as possible the relation between these vitamins and thyroid and iodine metabolism.—A. T. C.

Conditioned reflexes in thyroidectomized animals. I. (Bedingte Reflexe bei thyreoidektomierten Tieren. I). Asimoff, G., Arch. f. d. ges. Physiol. **220**: 350. 1928.

Young thyroidectomized dogs show reflexes conditioned from electric stimuli in like time with normal animals, but they do not have the characteristic efficiency of the latter; secondary reflexes were produced more difficultly. There was only slight improvement with lapse of time.—A. T. C.

Investigations on gas metabolism in recovery from exercise in healthy and sick children (Gaswechseluntersuchungen uber die Erholung nach Arbeit bei einigen gesunden und granken Kindern). Bruch, H., Jahrb. f. Kinderh. **121**: 7. 1928.

Exercise experiments were carried out with the aid of the Krogh spirometer and the sack method of Douglas and Haldane in 5 children. In a healthy 13 year old boy there was an increase in oxygen consumption, especially with an increase in the amount of work. One child with a hypofunction of the thyroid, and a corresponding low metabolic rate, showed a lowered energy requirement. In comparing this with values obtained in a normal child, it was found that the difference in oxygen consumption during the rest period was not great. The metabolic changes in the myxedematous child simulated those present in a normal child at rest. Similar findings were obtained in an obese child.—M. G. B.

The effect of iodin upon experimental hyperthyroidism in man. Carson, D. A. and W. Dock, Am. J. M. Sc. **176**: 701. 1928.

Four cases of human hyperthyroidism with all the attendant symptoms were induced by thyroid medication. Upon the administration of Lugol's solution, two of the patients had no lowering of the basal metabolism. There was a very slight drop in the basal metabolic rate in the first patient, and in the second there was no fall.—E. L.

Myocardial disturbances due to abnormal thyroid function and their management. Christian, H. A., Penn. M. J. **32**: 70. 1928.

The frequency of myocardial disturbances associated with abnormal thyroid function varies with the type of the latter. The possibility of later or subsequent cardiac lesions is a vital reason for prompt attention to the basic hyperthyroidism, whether associated with adenomatous or hyperplastic thyroid. Hypothyroidism should likewise receive early attention by appropriate thyroid opotherapy. Goiter not associated with disturbance of thyroid function requires no treatment with respect to prophylaxis of heart disease.—I. B.

Thyroid treatment of alopecia areata. Gordon, M. B., Arch. Dermat. & Syph. **17**: 817. 1928.

A case of almost complete alopecia in a young girl is reported. The condition had persisted for nine months in spite of local treatment. The administration of thyroid extract was followed by an immediate improvement, which continued until practically all of the hair had returned. The treatment consisted of thyroid extract, 1/10 gr. twice a day for one week, followed by a period of one week in which no extract was given. The dosage was then increased gradually to ⅛ gr., ¼ gr., ½ gr. and 1 gr., at first twice a day, then three times a day, the weekly alteration being adhered to.—Author's Abst.

Morphological changes in exophthalmic goiter following the use of Lugol's solution. Hellwig, C. A., Surg. Gynec. Obst. **47**: 173. 1928.

In thirty cases of exophthalmic goiter the thyroids were removed after Plummer's treatment and compared with thirty glands removed without previous iodine medication. Most of the observations described by Rienhoff could not be confirmed. After Plummer's treatment no changes in the vascularity and in the amount of fibrous tissue were found. The acini were not round, smooth-walled or of regular size and form. Neither was the epithelium flat and cuboidal, nor were the nuclei small, irregular and pyknotic. In 84% of the glands removed after Plummer's treatment the only definite difference as compared to untreated cases was found in the appearance of the colloid. The acini of these glands had more and higher concentrated content in spite of the fact that the hyperplastic character of the glands was not altered. These findings corroborate Albert Kocher's observation that in Basedow's disease most of the glands removed after iodine medication show distinctly more stained colloid.—Author's Abst.

Chemical studies on endemic goiter in Formosa. Hirohata, R., O. Watanabe and S. Watarai, J. Formosan Med. Soc. No. 276. 1928. Abst., Japan M. World, **8**: 216.

The author reports epidemiological, clinical and therapeutic studies on goiter occurring endemically in Formosa. In certain districts there occurred some 1.96 to 32.1%. There is one region in which two-thirds of the inhabitants suffered from the disease. In the therapy of the disease, he concludes that iodine seemed to be most efficacious. He also recommends the use of iodine for prophylactic use.

Juvenile exophthalmic goiter. McGraw, A. G., Surg. Gynec. Obst. **47**: 25. 1928.

Details, including surgical treatment, are given of two subjects, girls of 6 and 7 years, respectively. Sixty-four cases in the literature are analyzed. The identical nature of juvenile Graves' disease with that of the adult is stressed, along with the importance of following up over a long period of years the effects of operation in such cases.—A. T. C.

Relative lymphocytosis in hyperthyroidism. Menkin, V., Arch. Int. Med. **42**: 419. 1928.

Relative lymphocytosis was observed in 67% of the cases of hyperthyroidism. Relative lymphocytosis is more frequently seen in patients who have exophthalmos superimposed on the usual clinical signs of hyperthyroidism. In patients with exophthalmos, thyroidectomy decreases the relative lymphocytosis and restores a normal differential formula. It is suggested that the relative lymphocytosis in cases of exophthalmic goiter is due to sympathetic stimulation of lymphoid structures, particularly of the spleen, which causes it to contract, as evidenced by experimental work reported in a previous publication. Some patients with hyperthyroidism but without signs of exophthalmos show a relative lymphocytosis apparently not relieved by thyroidectomy. The mechanism of this type of relative lymphocytosis is not clear. It is suggested that it may be caused by a concomitant hyperplasia of lymphoid structures, such as the thymus.—Author's Summary.